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2nd world congress MATERNAL FETAL NEONATAL MEDICINE

CO-PLENARY SESSION 2: ENVIROMENTAL TOXICANTS AND REPRODUCTION

Chairpersons: ***Paolo Vineis, UK; Maria Dolores Gomez Roig, Spain***

Environmental carcinogenesis and trasgenerational trasmission of carcinogenic risk: from genetics to epigenetics

Ernesto Burgio, italy

ECERI - European Cancer and Environment Research Institute

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4TH – 6TH APRIL | 2019

First European Cancer and Environment Research Institute Workshop

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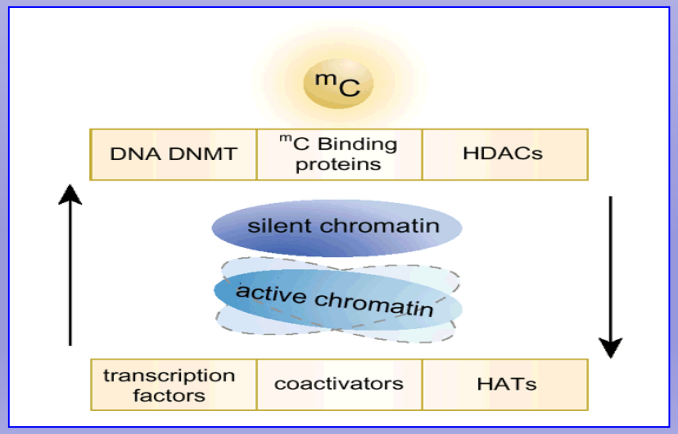
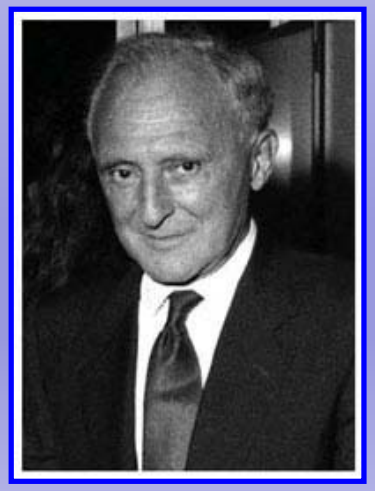
October the 26th 2012,
Académie Royale de Médecine de Belgique,
Belgium Royal Academy of Medicine,
Salle Albert I,
Brussels, Belgium

Notes on the epigenetic (transplacental and transgenerational) origins of childhood cancer

ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute





I decided to begin my report this year with this slide (of a few years ago) that is a tribute **to Renzo Tomatis, a great experimental oncologist, the former director of the IARC, who was among the first in the world to guess what was happening in the field of childhood cancers** and whot helped me understand it..

As we can easily assume from the title of this paper, published on the NCI Monographs, Renzo had **already understood over 40 years ago** (studying the drama of Dietilstlbestrol ..) the great risk of an **ongoing increase of chronic diseasess (and above all of childhood cancers) in the generations following those exposed, in utero, to a growing number of pollutants** ..

A continuous increase that is occurring all over the world, and that **we are doing nothing yet to prevent**

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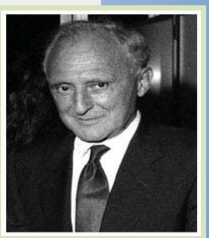
1: Natl Cancer Inst Monogr. 1979 May;(51):159-84.



Prenatal exposure to chemical carcinogens and its effect on subsequent generations.

Tomatis L.

1

That exposure of pregnant animals to chemical carcinogens results in the occurrence of tumors in the progeny is well documented. Evidence has been accumulated on at least 38 chemicals pertaining to different chemical groups. The experimental evidence was followed by 2 observations in humans regarding the increased risk of cancer in daughters of women who received stilbestrol during pregnancy. Additional experimental evidence is accumulating on the possibility that exposure during pregnancy results in an increased incidence of tumors for more 3 than one generation of untreated descendants. Studies done on mice with DMBA and on rats with MNU and ENU showed that exposure to the carcinogens during pregnancy resulted in a high incidence of tumors in animals of the first generation and in an increased incidence of tumors at specific sites in untreated animals of the second and third generations.

PMID: 384260 [PubMed - indexed for MEDLINE]

I tumori in Italia • Rapporto AIRTUM 2012 • TUMORI INFANTILI

Ernesto Burgio

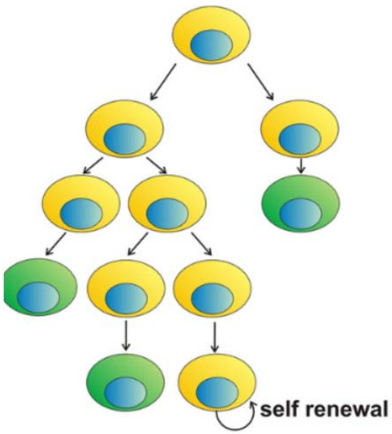
Capitolo 3.4

Epidemiol Prev 2013; 37 (1) suppl 1: 1-296

Brevi note sulle origini epigenetiche dei tumori infantili

Notes on the epigenetic origins of childhood cancer

The stochastic model

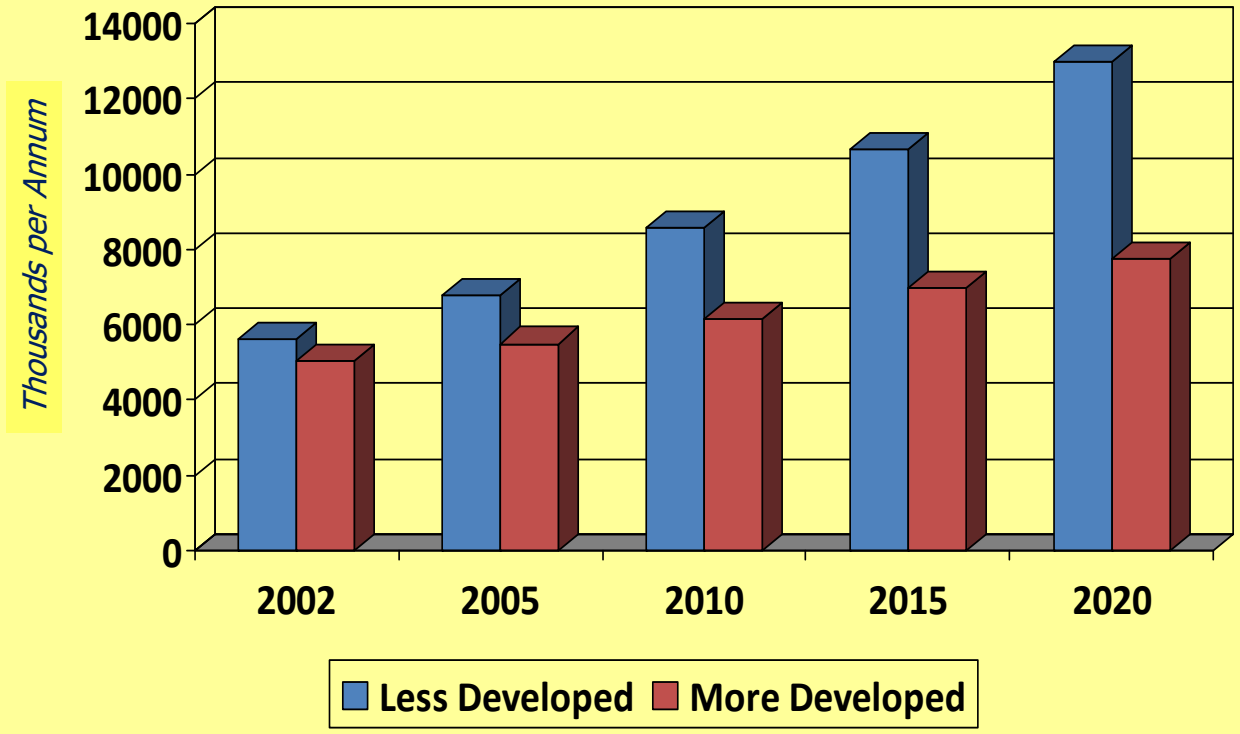


Cancer is generally associated with **old age** and its **continuous increase, observed throughout the 20th century** in all the industrialized countries, **is often explained** by the **theory of the progressive accumulation of DNA stochastic mutations (SMT)**

Cancer is generally associated with old age, and its continuous increase observed throughout the 20th century in all industrialized Countries is often explained as a consequence of progressive accumulation of oxidative, stochastic (random) genetic damage, along with ongoing improvement in our diagnostic capacities. The fact that the increase, from the end of the 1980s to 2000, has involved individuals of all ages, young people included, has been too often underestimated. Recent reports of a significant increase in childhood cancer in Europe[1] and especially Italy has caused concern, forcing us to critically reconsider this dominant model of carcinogenesis.[2,3]

the significant increase in the Less Developed Countries & in young people all over the world demonstrates the limits of the SMT (→necessary link between *aging* &CA)

The recent **IARC reports***
Concerning a significant **ongoing increase** of **cancer** in children (infants **included) is causing concern,** forcing scientists to reconsider the **dominant model of carcinogenesis..**

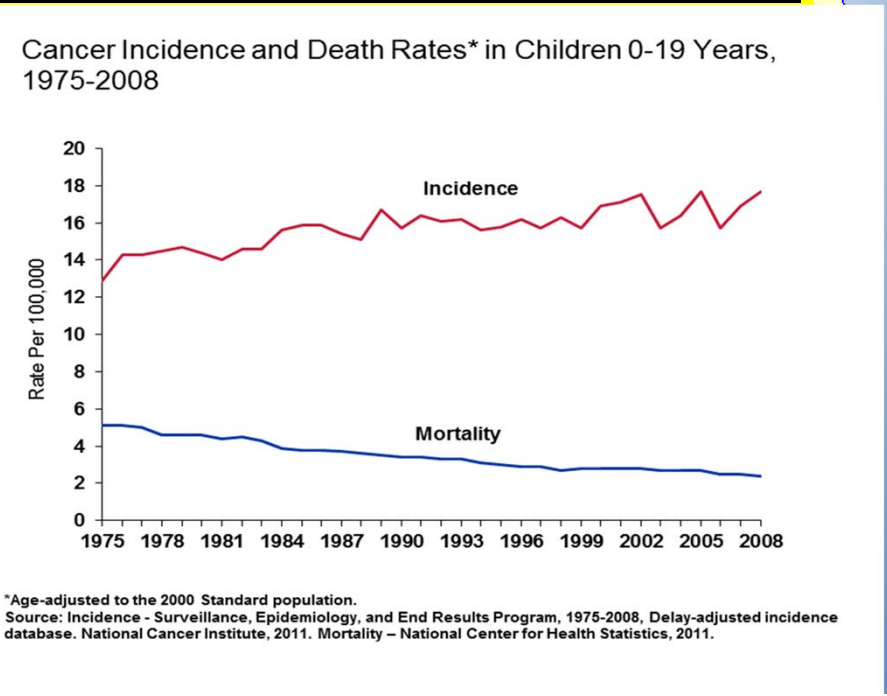


**** ACCIS (Automated Childhood Cancer Information System)*** is a comprehensive monitoring **conducted by a team of IARC epidemiologists on 63 cancer registries from 19 European countries**..

(2) Children cancer increase

Child cancers are generally considered as a **rare disease**. **But** it is worth remembering

- *that*, statistically, **about 1 in 5-600 children will develop cancer before the age of 15**;
- *that*, in spite of the decisive improvement in diagnosis and therapy in the last decades, **cancer** is **the leading cause of death due to diseases among children over the first year of age**;
- *that*, **even at this age, a continuous and significant increase has been seen during the last decades.**



TEN LEADING CAUSES OF DEATH

(Children aged under 15 years) U.S. 2006

RANK	CAUSE OF DEATH	NO. OF DEATHS	% OF TOTAL DEATHS	DEATH RATE*
	ALL CAUSES	10780	100.0	19.0
1	Accidents (unintentional injuries)	3868	35.9	6.8
2	Cancer	1284	11.9	2.3
3	Congenital anomalies	859	8.0	1.5
4	Assault (homicide)	756	7.0	1.3
5	Heart diseases	414	3.8	0.7
6	Intentional self-harm (suicide)	219	2.0	0.4
7	Influenza & pneumonia	193	1.8	0.3
8	Septicemia	172	1.6	0.3
9	Chronic lower respiratory diseases	158	1.5	0.3
10	Cerebrovascular disease	149	1.4	0.3
	All other causes	2708	25.1	-

* Rates are per 100,000 population and age adjusted to the 2000 US standard population.

Cancer is **the leading cause of death by disease** in children after the first year of age

Based on US Mortality Data, 2006, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009

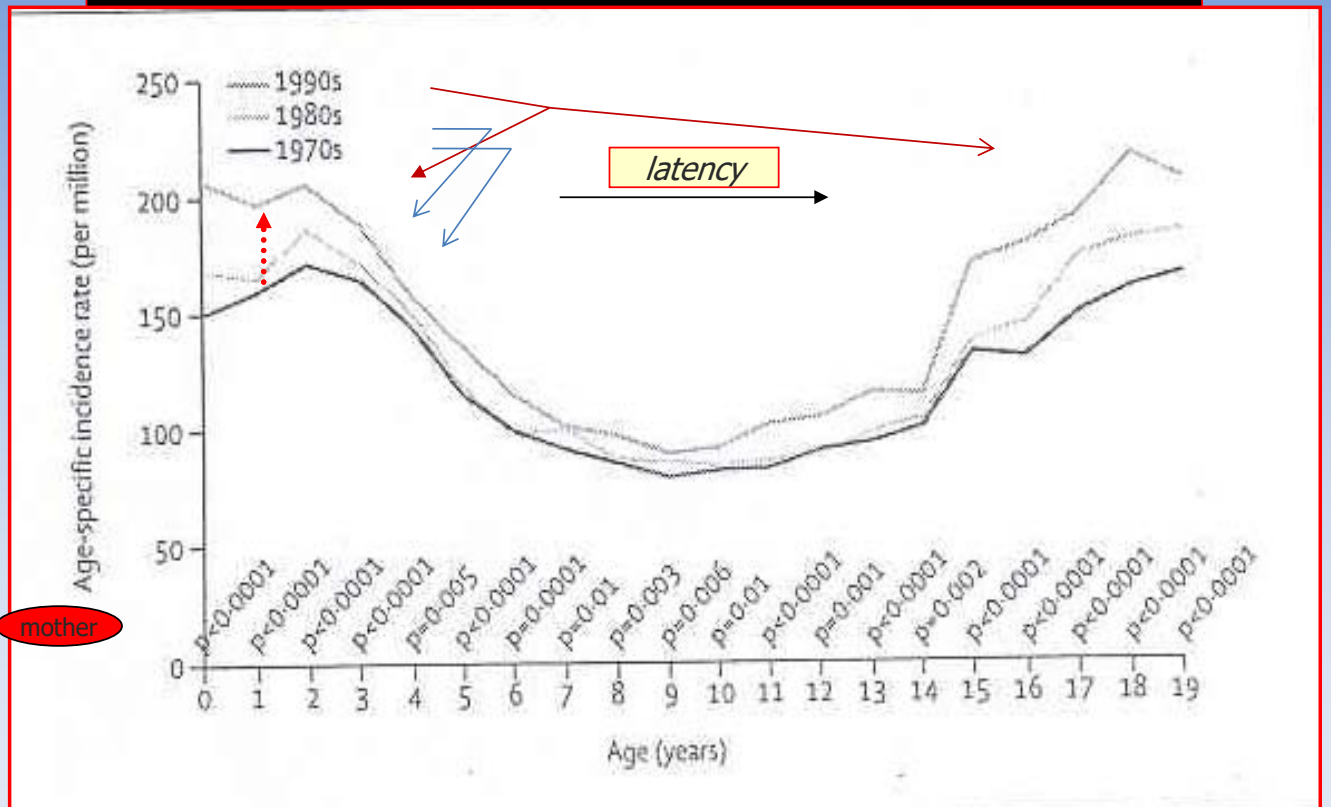
A first draft of the report, published on *the Lancet* in 2004, demonstrated an annual increase of 1-1,5% for all cancers (with more marked increases in lymphomas, soft tissue sarcomas, tumours of the nervous system…)
But the most troubling was the increase - **almost the double - for all cancers in the very first year of life (apparently due to *transplacental* or even *trans-generational* exposure)**

http://www-dep.iarc.fr/accis.htm

CA incidence in childhood and adolescence IN EUROPE (1970-1999)

The ***ACCIS (Automated Childhood Cancer Information System) first phase (1970-1999)*** concerned **over *130 thousand tumors* of all types** (113 thousand children and 18 thousand teenagers)…

..as for the years ***1991–2010***, 53 registries in 19 countries contributed a total of ***180.335 cases…***



Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, Parkin M. *Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study.* Lancet. 2004 Dec 11-17;364(9451):2097-105

The first data from the ACCIS project published in *the Lancet* were soon confirmed by the next review of the data (the most complete to date) which has become the largest European database on children cancer, published two years later on the *European Journal of Cancer* (18 items in all, containing detailed analysis of data on incidence rates and trends of prevalence and survival)..

EUROPEAN JOURNAL OF CANCER 42 (2006) 1961–1971

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journal homepage: www.ejconline.com

Time trends of cancer incidence in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

Peter Kaatsch[a,*], *Eva Steliarova-Foucher*[b], *Emanuele Crocetti*[c], *Corrado Magnani*[d], *Claudia Spix*[a], *Paola Zambon*[e]

[a]German Childhood Cancer Registry (GCCR), Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University of Mainz, 55101 Mainz, Germany
[b]Descriptive Epidemiology Group, International Agency for Research on Cancer (IARC), Lyon, France
[c]Tuscany Cancer Registry, Firenze, Italy
[d]Childhood Cancer Registry of Piedmont, CPO-Piemonte, CERMS and University of East Piedmont, Novara, Italy
[e]Veneto Cancer Registry University of Padua, IOV, Italy

A B S T R A C T

Within the framework of the Automated Childhood Cancer Information System (ACCIS), time trend analyses for childhood cancer were performed using data from 33 population-based cancer registries in 15 European countries for the period 1978–1997. The overall incidence rate based on 77,111 cases has increased significantly ($P < 0.0001$), with an average annual percentage change (AAPC) of 1.1%. The rising trend was observed in all five geographical regions and in the majority of the disease groups (in order of AAPC): soft tissue sarcomas (1.8%), brain tumours, tumours of the sympathetic nervous system, germ-cell tumours, carcinomas, lymphomas, renal tumours, and leukaemias (0.6%). No change was seen in incidence of bone tumours, hepatic tumours and retinoblastoma. The increased incidence can only partly be explained by changes in diagnostic methods and by registration artefacts. The patterns and magnitude of these increases suggest that other factors, e.g. changes in lifestyle and in exposure to a variety of agents, have contributed to the increase in childhood cancer in the recent decades.

..in the last 20 years (1978 e il 1997) the overall incidence rate has increased significantly with an average annual percentage change (AAPC) of 1,1% (> 2% in the first year; 1,3 % during adolescence).

Table 4 – Average annual percent of change (AAPC) and result of trend test for childhood cancer (age 0–14 years) in Europe by age groups and sex for total cancer and main diagnostic groups (*P < 0.05; ** P < 0.01; *** P < 0.0001) (1978–1997) (Source: ACCIS)

	AAPC for diagnostic groups												AAPC for total (%)
	Leu (%)	Ly (%)	CNS (%)	Symp (%)	Ret (%)	Ren (%)	Hep (%)	Bone (%)	Soft (%)	Germ (%)	Ca (%)	Oth (%)	
Age 0	0.6	–1.6	2.4***	2.2***	0.9	1.9*	1.5	–7.4	1.3	3.9***	–0.4	3.2	2.1***
Age 1–4 years	0.7***	0.6	1.8***	1.7***	0.4	0.8*	1.2	–0.5	1.9***	–0.1	0.6	–0.2	1.1***
Age 5–9 years	0.5*	0.7	1.6***	0.1	–0.6	0.5	–1.8	–1.2	1.3*	0.90	–0.9	1.0	0.8***
Age 10–14 years	0.5*	1.3***	1.7***	1.9	–6.0	0.5	0.3	0.2	2.6***	2.5***	2.2***	1.7	1.3***
Male	0.7***	0.5*	1.5***	1.5***	0.3	0.4	0.9	–0.3	1.7***	1.2*	1.2	0.2	0.9***
Female	0.6**	1.7***	2.0***	2.0***	0.7	1.3**	0.6	–0.2	2.0***	2.0***	1.3*	2.0	1.4***

Leu, leukaemias; Ly, lymphomas; CNS, CNS tumours; Symp, tumours of the sympathic nervous system; Ret, retinoblastoma; Ren, renal tumours; Hep, hepatic tumours; Bone, malignant bone tumours; Soft, soft tissue sarcomas; Germ, germ-cell tumours; Ca, carcinomas; Oth, other and unspecified malignant neoplasms.

These data should not be underestimated for at least 4 reasons:

- the **large size of the study sample** (**63 cancer registries** from **19 European countries**, for a total of **more than 130000 cancers of all kinds**: **113000** strictly paediatric and 18000 teenager cancers);
- a **sufficiently prolonged period of observation (20 years);**
- **a maximum increase in the first year of age**, which suggests a ***transplacental*** (from maternal and fetal exposure to pro-carcinogenic agents) **or even a *transgenerational* (*epigenetic/gametic*) origin;**
- **the concomitant increase** in the whole northern hemisphere of a variety of **chronic-degenerative and inflammatory diseases** (endocrine-metabolic: **obesity, type 2 diabetes**; immune-mediated: **allergies, autoimmune diseases**, neuro-development and neuro-degenerative diseases: **autism, ADHD, Alzheimer's disease**..) **for all of which** a significant pathogenic role of the **mechanisms of early epigenetic dysregulation (*fetal programming*)** on various organs and tissues **has recently been suggested (*DOHaD-Developmental Origins of Health and Diseases*).**

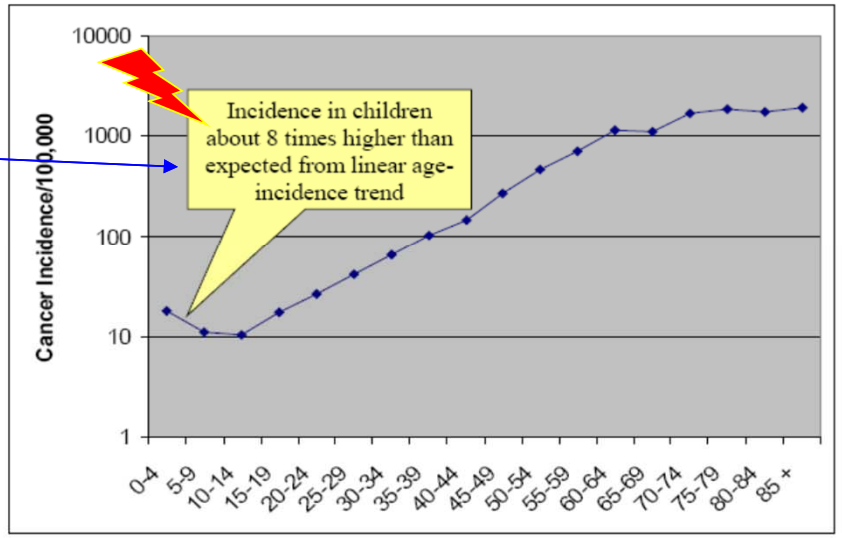
For the years ***1991–2010,*** 53 registries in 19 countries contributed a total of ***180 335 unique cases…***

Gluckman PD, Hanson MA. ***Developmental origins of disease paradigm: a mechanistic and evolutionary perspective.*** Pediatr. Res. (2004); 56:311–17

Cancers in *adults* predominantly arise in (epithelial) tissues chronically exposed to *environmental stress* and **in cells and tissues continually urged to respond/react to it**

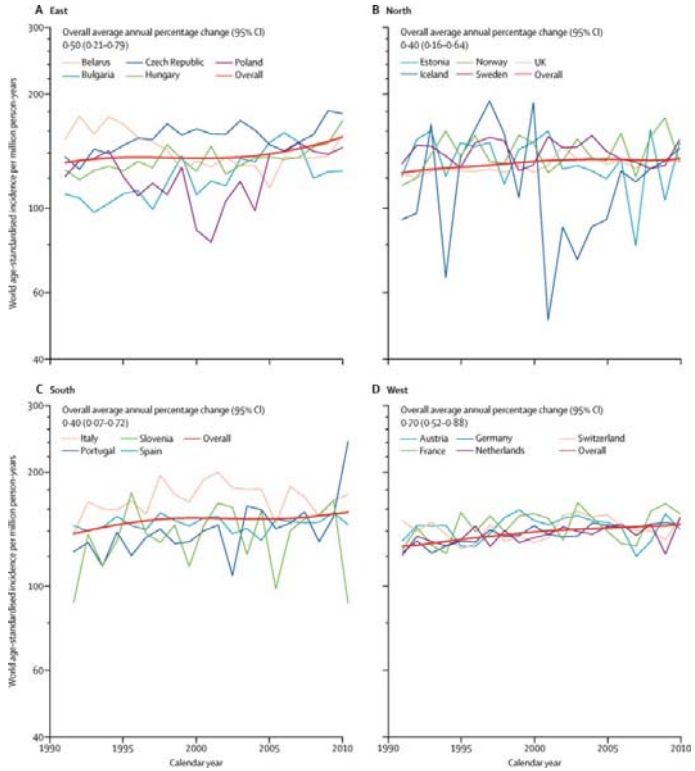
While almost all ***childhood cancers*** belong to three major groups:
45% oncohaematologic tumors (leukemias and lymphomas)
25% **brain** tumors
25% neoplastic degeneration of ***embryonal residuals***

The **increase** particularly affects children in their **first life year (the incidence rate increased by > 2%/year)**



THE LANCET
Oncology
Volume 19, Issue 9, September 2018, Pages 1159-1169

A few months ago we found in ***The Lancet Oncology*** **the last confirmation** of the validity of these dramatic data



Articles

Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991–2010 (Automated Childhood Cancer Information System): a population-based study

Eva Steliarova-Foucher PhD [a], Miranda M Fidler PhD [a], Murielle Colombet MSc [a], Brigitte Lacour MD [b, c], Peter Kaatsch PhD [d], Marion Piñeros MD [a], Isabelle Soerjomataram PhD [a], Freddie Bray PhD [a], Prof Jan Willem Coebergh PhD [e], Rafael Peris-Bonet PhD [f], Charles A Stiller MSc [g]

The combined age-standardised incidence of leukaemia based on 48 458 cases in children was 46·9 (46·5–47·3) per million person-years and increased significantly by 0·66% (0·48–0·84) per year. The average overall incidence of leukaemia in adolescents was 23·6 (22·9–24·3) per million person-years, based on 4702 cases, and the average annual change was 0·93% (0·49–1·37). We also observed increasing incidence of lymphoma in adolescents (average annual change 1·04% [0·65–1·44], malignant CNS tumours in children (average annual change 0·49% [0·20–0·77]), and other tumours in both children (average annual change 0·56 [0·40–0·72]) and adolescents (average annual change 1·17 [0·82–1·53]).

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International Journal of
Environmental Research and Public Health

Int J Environ Res Public Health. (2018) 20;15(8)

Also because of these data we were **requested to write this review,** in which we proposed **a comprehensive critical analysis of the current model of carcinogenesis (SMT)**

Editorial

Environmental Carcinogenesis and Transgenerational Transmission of Carcinogenic Risk: From Genetics to Epigenetics

Ernesto Burgio [1,2], Prisco Piscitelli [2,*] and Annamaria Colao [3]

1 European Cancer and Environment Research Institute (ECERI), 1000 Bruxelles, Belgium; erburg@libero.it
2 Euro Mediterranean Scientific Biomedical Institute (ISBEM), 72023 Mesagne, Brindisi, Italy
3 Department of Clinical Medicine and Surgery, University Federico II School of Medicine, 80138 Naples, Italy; colao@unina.it
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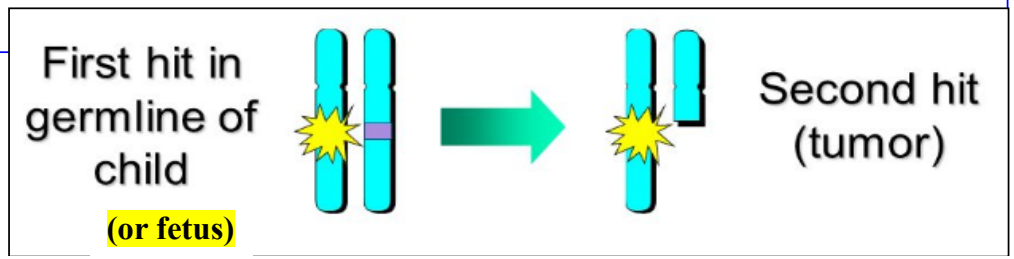
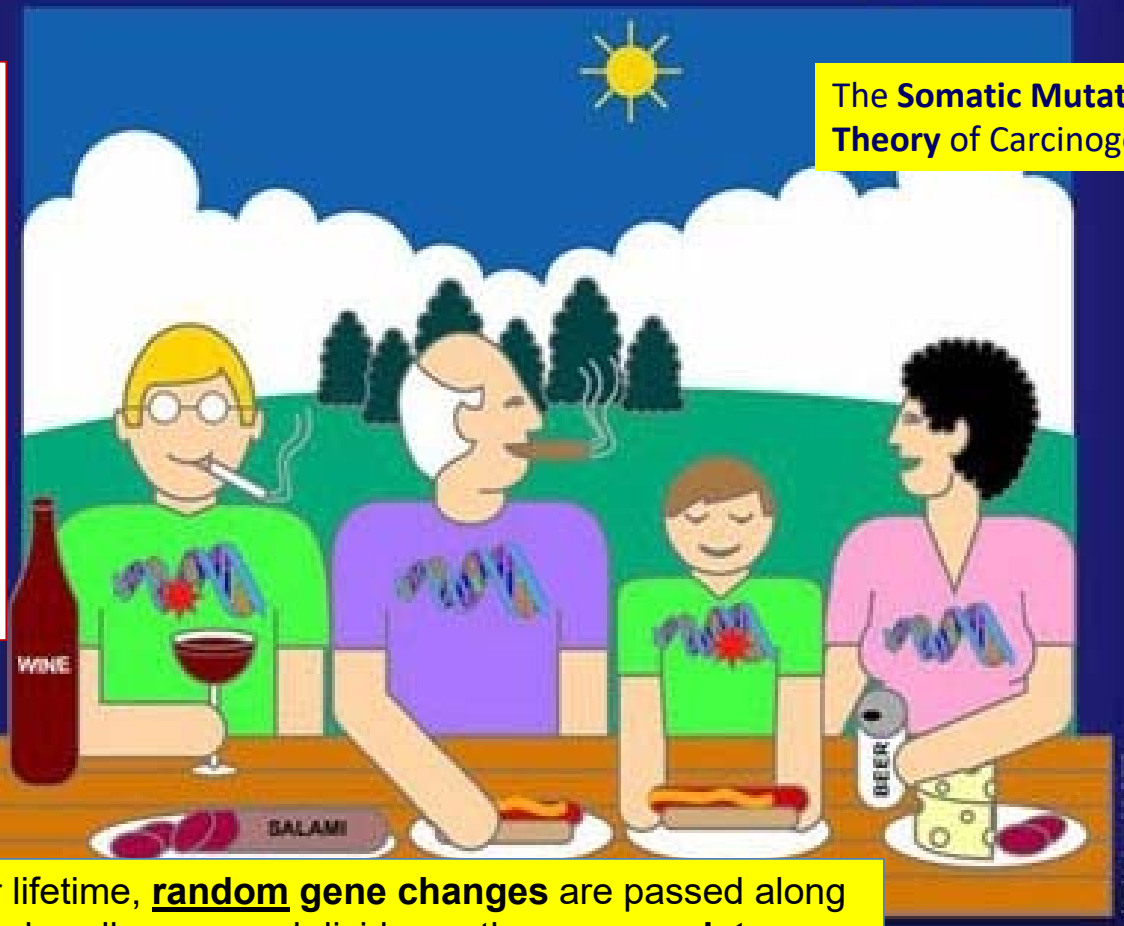
.. the most powerful procarcinogenic mechanisms of EDCs and other pollutants is linked to their **potential to interfere epigenetically with the embryo-fetal programming of tissues and organs**, altering the regulation of the **genes involved in the cell cycle, cell proliferation, apoptosis, and other key signaling pathways.** The **embryo-fetal exposure to environmental, stressful, and proinflammatory triggers (first hit), seems to act as a *'disease primer'*,** making fetal cells and tissues more susceptible to **the subsequent environmental exposures (second hit), triggering the carcinogenic pathways.**



What is Cancer ?

The Inside Matters: Random Gene Changes



The **Somatic Mutation Theory** of Carcinogenesis

This increase is in **clear (and so far completely underestimated) contrast with the dominant models of carcinogenesis (SMT)** according to which **cancer is essentially a genetic "accident" due to stochastic DNA mutations…** **and for this reason largely prevalent in the elderly**

Over your lifetime, **random gene changes** are passed along as your body cells grow and divide, so they **accumulate**

CELEBRATING OUR TENTH YEAR
HISTORICAL PERSPECTIVE
nature medicine

What's *Cancer* ?

Cancer genes and the pathways they control

Bert Vogelstein & Kenneth W Kinzler

The revolution in cancer research can be summed up in a single sentence: **cancer is, in essence, a *genetic* disease**

The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease. In the last decade, many important genes responsible for the genesis of various cancers have been discovered, their mutations precisely identified, and the pathways through which they act characterized. The purposes of this review are to highlight examples of progress in these areas, indicate where knowledge is scarce and point out fertile grounds for future investigation.

Alterations in three types of genes are responsible for tumorigenesis:
oncogenes, ***tumor-suppressor genes*** and ***stability genes***
Unlike diseases such as cystic fibrosis or muscular dystrophy,
wherein mutations in one gene can cause disease, no single gene defect 'causes' cancer. Mammalian **cells have multiple safeguards to protect them against the potentially lethal effects of cancer gene mutations**,
and **only when several genes are defective does an invasive cancer develop**

Vogelstein B, Kinzler KW. ***Cancer genes and the pathways they control*** Nat Med. 2004 Aug;10(8):789-99.

Table 1 Cancer predisposition genes

Gene (synonym(s))[a]	Syndrome	Hereditary pattern	Second hit	Pathway[b]	Major heredity tumor types[c]
Tumor-suppressor genes					
APC	FAP	Dominant	Inactivation of WT allele	APC	Colon, thyroid, stomach, intestine
AXIN2	Attenuated polyposis	Dominant	Inactivation of WT allele	APC	Colon
CDH1 (E-cadherin)	Familial gastric carcinoma	Dominant	Inactivation of WT allele	APC	Stomach
GPC3	Simpson-Golabi-Behmel syndrome	X-linked	?	APC	Embryonal
TP53 (*p53*)	Li-Fraumeni syndrome	Dominant	Inactivation of WT allele	p53	Breast, sarcoma, adrenal, brain...
WT1	Familial Wilms tumor	Dominant	Inactivation of WT allele	p53	Wilms'
STK11 (*LKB1*)	Peutz-Jeghers syndrome	Dominant	Inactivation of WT allele	PI3K	Intestinal, ovarian, pancreatic
PTEN	Cowden syndrome	Dominant	Inactivation of WT allele	PI3K	Hamartoma, glioma, uterus
TSC1, TSC2	Tuberous sclerosis	Dominant	Inactivation of WT allele	PI3K	Hamartoma, kidney
CDKN2A (*p16*^{INK4A}, *p14*^{ARF})	Familial malignant melanoma	Dominant	Inactivation of WT allele	RB	Melanoma, pancreas
CDK4	Familial malignant melanoma	Dominant	?	RB	Melanoma
RB1	Hereditary retinoblastoma	Dominant	Inactivation of WT allele	RB	Eye
NF1	Neurofibromatosis type 1	Dominant	Inactivation of WT allele	RTK	Neurofibroma
Stability genes					
MUTYH	Attenuated polyposis	Recessive	?	BER	Colon
ATM	Ataxia telangiectasia	Recessive	?	CIN	Leukemias, lymphomas, brain
BLM	Bloom syndrome	Recessive	?	CIN	Leukemias, lymphomas, skin
BRCA1, BRCA2	Hereditary breast cancer	Dominant	Inactivation of WT allele	CIN	Breast, ovary
FANCA, C, D2, E, F,G	Fanconi anemia	Recessive	?	CIN	Leukemias
MSH2, MLH1, MSH6, PMS2	HNPCC	Dominant	Inactivation of WT allele	MMR	Colon, uterus
XPA, C; ERCC2–5; DDB2	Xeroderma pigmentosum	Recessive	?	NER	Skin
Oncogenes					
KIT	Familial gastrointestinal stromal tumors	Dominant	?	RTK	Gastrointestinal stromal tumors
MET	Hereditary papillary renal cell carcinoma	Dominant	Mutant allele duplication	RTK	Kidney

Cell
Volume 100, Issue 1, 7 January 2000, Pages 57-70

What's *Cancer* ?

Review

The Hallmarks of Cancer

Douglas Hanahan [1], and Robert A. Weinberg [2]

[1] Department of Biochemistry and Biophysics and, Hormone Research Institute, University of California at San Francisco, San Francisco, California 94143, USA

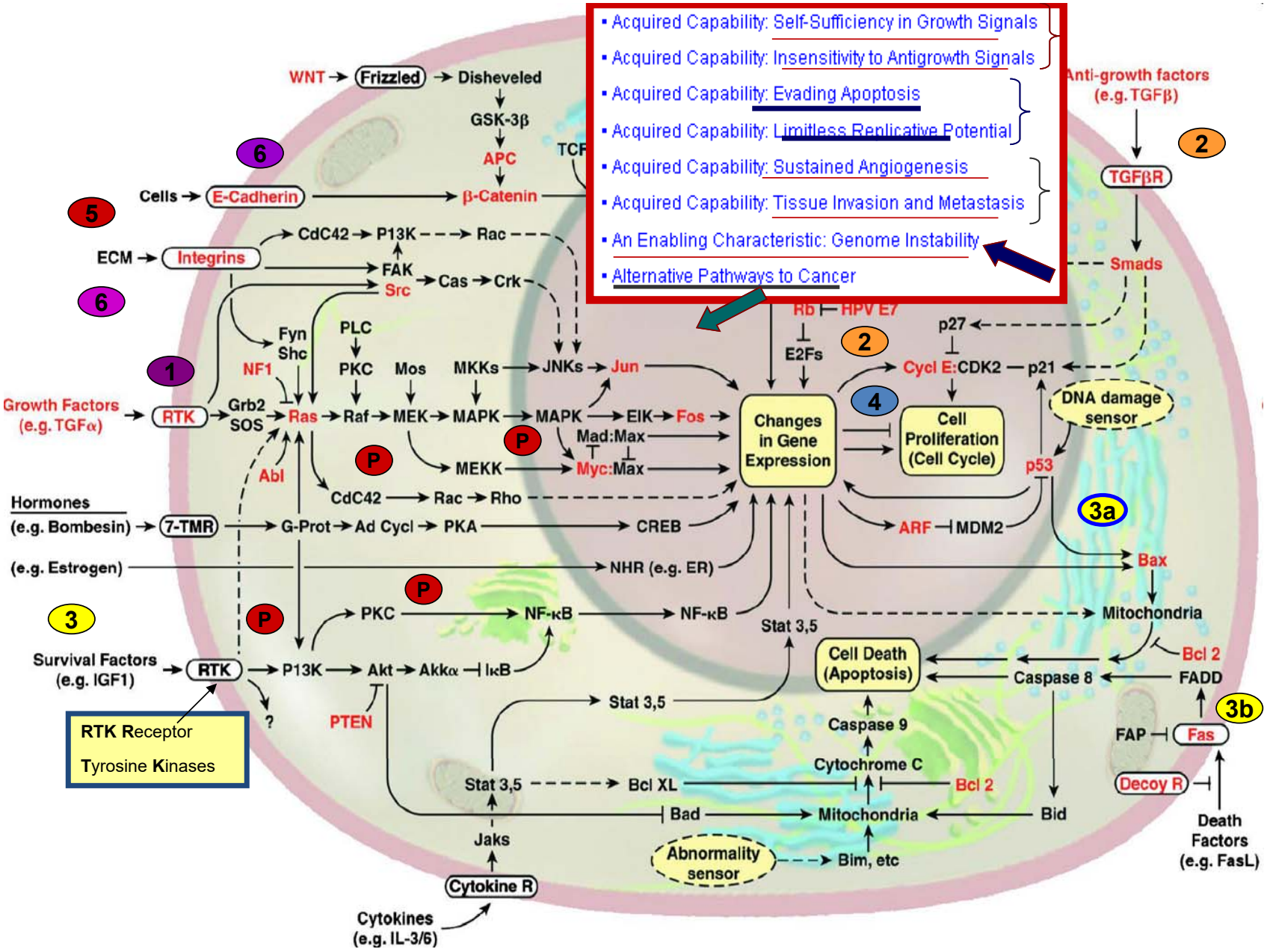
[2] Whitehead Institute for Biomedical Research and, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA

We suggest that **the vast catalogues of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth**

Tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of stochastic mutations, each conferring one or another type of **growth advantage**, leads to the progressive conversion of normal human cells into CA-cells…

CA-cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis… the vast catalog of CA-cell genotypes is a manifestation of **six essential alterations in cell physiology that collectively dictate malignant growth:**

- Acquired Capability: Self-Sufficiency in Growth Signals 1
- Acquired Capability: Insensitivity to Antigrowth Signals 2
- Acquired Capability: Evading Apoptosis 3
- Acquired Capability: Limitless Replicative Potential 4
- Acquired Capability: Sustained Angiogenesis 5
- Acquired Capability: Tissue Invasion and Metastasis 6
- An Enabling Characteristic: Genome Instability
- Alternative Pathways to Cancer


▪ Acquired Capability: Self-Sufficiency in Growth Signals
▪ Acquired Capability: Insensitivity to Antigrowth Signals
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▪ Acquired Capability: Limitless Replicative Potential
▪ Acquired Capability: Sustained Angiogenesis
▪ Acquired Capability: Tissue Invasion and Metastasis
▪ An Enabling Characteristic: Genome Instability
▪ Alternative Pathways to Cancer
WNT
Frizzled
Disheveled
GSK-3β
APC
β-Catenin
TCF
Cells
E-Cadherin
ECM
Integrins
CdC42
P13K
Rac
FAK
Src
Cas
Crk
Fyn
Shc
PLC
NF1
PKC
Mos
MKKs
JNKs
Jun
Growth Factors
(e.g. TGFα)
RTK
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
ElK
Fos
Mad:Max
Myc:Max
MEKK
Abl
CdC42
Rac
Rho
Hormones
(e.g. Bombesin)
7-TMR
G-Prot
Ad Cycl
PKA
CREB
(e.g. Estrogen)
NHR (e.g. ER)
Survival Factors
(e.g. IGF1)
RTK
P13K
Akt
Akkα
IκB
PKC
NF-κB
NF-κB
PTEN
?
Stat 3,5
Stat 3,5
Jaks
Cytokine R
Cytokines
(e.g. IL-3/6)
RTK Receptor
Tyrosine Kinases
Changes
in Gene
Expression
Rb
HPV E7
E2Fs
Cycl E:CDK2
p21
p27
Cell
Proliferation
(Cell Cycle)
DNA damage
sensor
p53
ARF
MDM2
Anti-growth factors
(e.g. TGFβ)
TGFβR
Smads
Bax
Mitochondria
Bcl 2
Cell Death
(Apoptosis)
Caspase 8
FADD
FAP
Fas
Decoy R
Death
Factors
(e.g. FasL)
Caspase 9
Cytochrome C
Bcl XL
Bcl 2
Bad
Mitochondria
Bid
Abnormality
sensor
Bim, etc
1
2
2
3
3a
3b
4
5
6
6
P
P
P

What are the hallmarks of cancer?

The seminal article by Douglas Hanahan and Robert Weinberg on the hallmarks of cancer is 10 years old this year and its contribution to how we see cancer has been substantial. But, in embracing this view, have we lost sight of what makes cancer cancer?

Yuri Lazebnik is at Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, New York, USA.
e-mail: lazebnik@cshl.edu

NATURE REVIEWS | CANCER
APRIL 2010 | VOLUME 10

some ***benign tumours*** *can weigh many* ***kilograms*** at the time of diagnosis

sustained angiogenesis is a feature of both benign and malignant tumours

RB protein is deficient both in retinoblastoma, a malignant tumour of the eye, and in ***retinoma***, a benign tumour of this organ.

evasion of apoptosis has been implicated in the pathogenesis of **malignant and benign** tumours

insensitivity to antigrowth signals and **evasion of cell death** also seem to be **characteristic of both benign and malignant tumours**

five of the proposed hallmarks of cancer **are also characteristic of** ***benign tumours***

The only distinguishing feature (HALLMARK) of cancer is its **ability to metastasize** (which is **not the result of mutations**, but the **reactivation of an embryonic genetic program !!)**

On the basis of these models it was possible, **even recently, to theorize that cancer is essentially bad luck…**

NEWS | IN DEPTH

2 JANUARY 2015 • VOL 347 ISSUE 6217

BIOMEDICINE

The bad luck of cancer

Analysis suggests most cases can't be prevented

By Jennifer Couzin-Frankel

Random mutations in healthy cells may explain two-thirds of cancers, like this one in the colon.

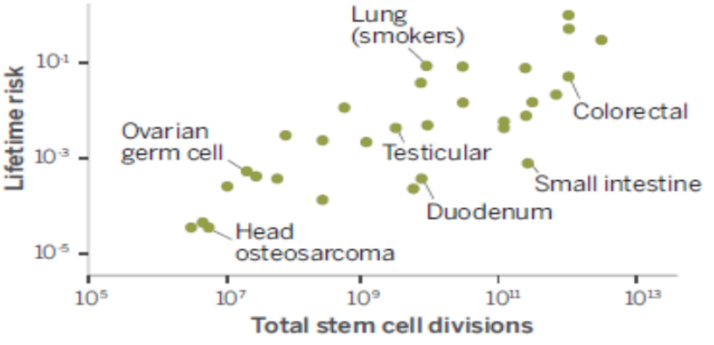
CANCER ETIOLOGY

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti[1]* and Bert Vogelstein[2]*

Charting cancer risk

As the number of stem cell divisions in a tissue rises, so does the chance of cancer striking that site.



NEWS FEATURE

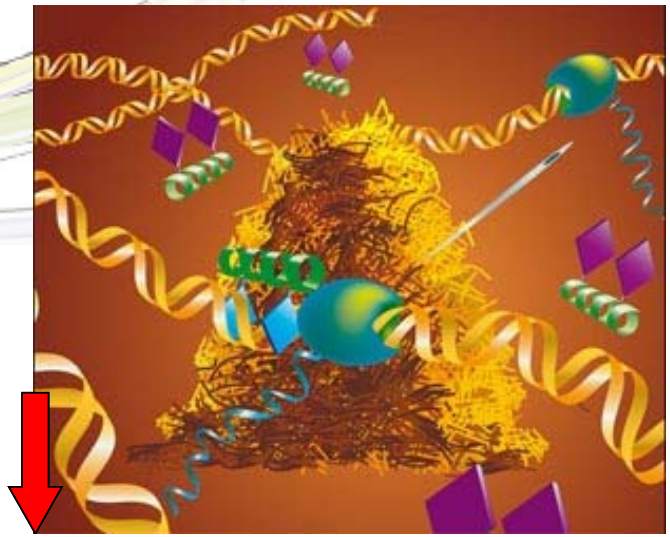
NATURE|Vol 464|15 April 2010

The GWAS efforts are certainly creating **bigger haystacks** …

The CANCER GENOME challenge

Databases could soon be flooded with genome sequences from 25,000 tumours. **Heidi Ledford** looks at the obstacles researchers face as they search for meaning in the data.

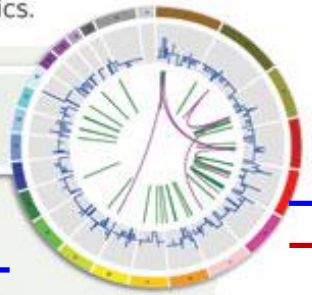
In a recent **editorial** on *Nature* Heidi Ledford stated that **the millions of genetic sequences and SNPs accumulated** in an attempt to **decipher the genetics of cancer** have built **giant haystacks in which researchers have gone lost …**



The full genome sequence of a lung cancer cell line, for example, yielded 22,910 point mutations, only 134 of which were in protein-coding regions

CANCER GENOMES COMING FAST

A few examples of fully and partially sequenced cancer genomes and their defining characteristics.



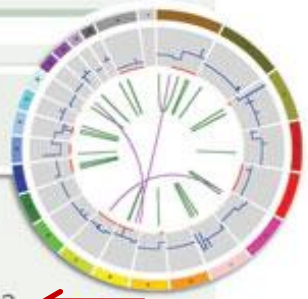
LUNG CANCER

Cancer: small-cell lung carcinoma

- Sequenced: full genome
- Source: NCI-H209 cell line
- Point mutations: 22,910
- Point mutations in gene regions: 134
- Genomic rearrangements: 58
- Copy-number changes: 334

Highlights:
Duplication of the *CHD7* gene confirmed in two other small-cell lung carcinoma cell lines.

Source: E. D. Pleasance *et al. Nature* **463,** 184–190 (2010).



SKIN CANCER

Cancer: metastatic melanoma

- Sequenced: full genome
- Source: COLO-829 cell line
- Point mutations: 33,345
- Point mutations in gene regions: 292
- Genomic rearrangements: 51
- Copy-number changes: 41

Highlights:
Patterns of mutation reflect damage by ultraviolet light.

Source: E. D. Pleasance *et al. Nature* **463,** 191–196 (2010).

BREAST CANCER

Cancer: basal-like breast cancer

- Sequenced: full genome
- Source: primary tumour, brain metastasis, and tumours transplanted into mice
- Point mutations: 27,173 in primary, 51,710 in metastasis and 109,078 in transplant
- Point mutations in gene regions: 200 in primary, 225 in metastasis, 328 in transplant
- Genomic rearrangements: 34
- Copy-number changes: 155 in primary, 101 in metastasis, 97 in transplant

Highlights:
The *CTNNA1* gene encodes a putative suppressor of metastasis that is deleted in all tumour samples.

Source: L. Ding *et al. Nature* **464,** 999–1005 (2010).

BRAIN CANCER

Cancer: glioblastoma multiforme

- Sequenced: exome (no complete Circos plot)
- Source: 7 patient tumours, 15 tumours transplanted into mice (follow-up sequencing on 21 genes for 83 additional samples)
- Genes containing at least one protein-altering mutation: 685
- Genes containing at least one protein-altering point mutation: 644
- Copy-number changes: 281

Highlights:
Mutations in the active site of *IDH1* have been found in 12% of patients.

Source: E. R. Mardis *et al. N. Engl. J. Med.* **361,** 1058–1066 (2009).

3RD INTERNATIONAL
Cancer Control Congress

INTERNATIONAL COLLABORATIONS | 8-11 NOVEMBER 2009 / CERNOBBIO, COMO, ITALY

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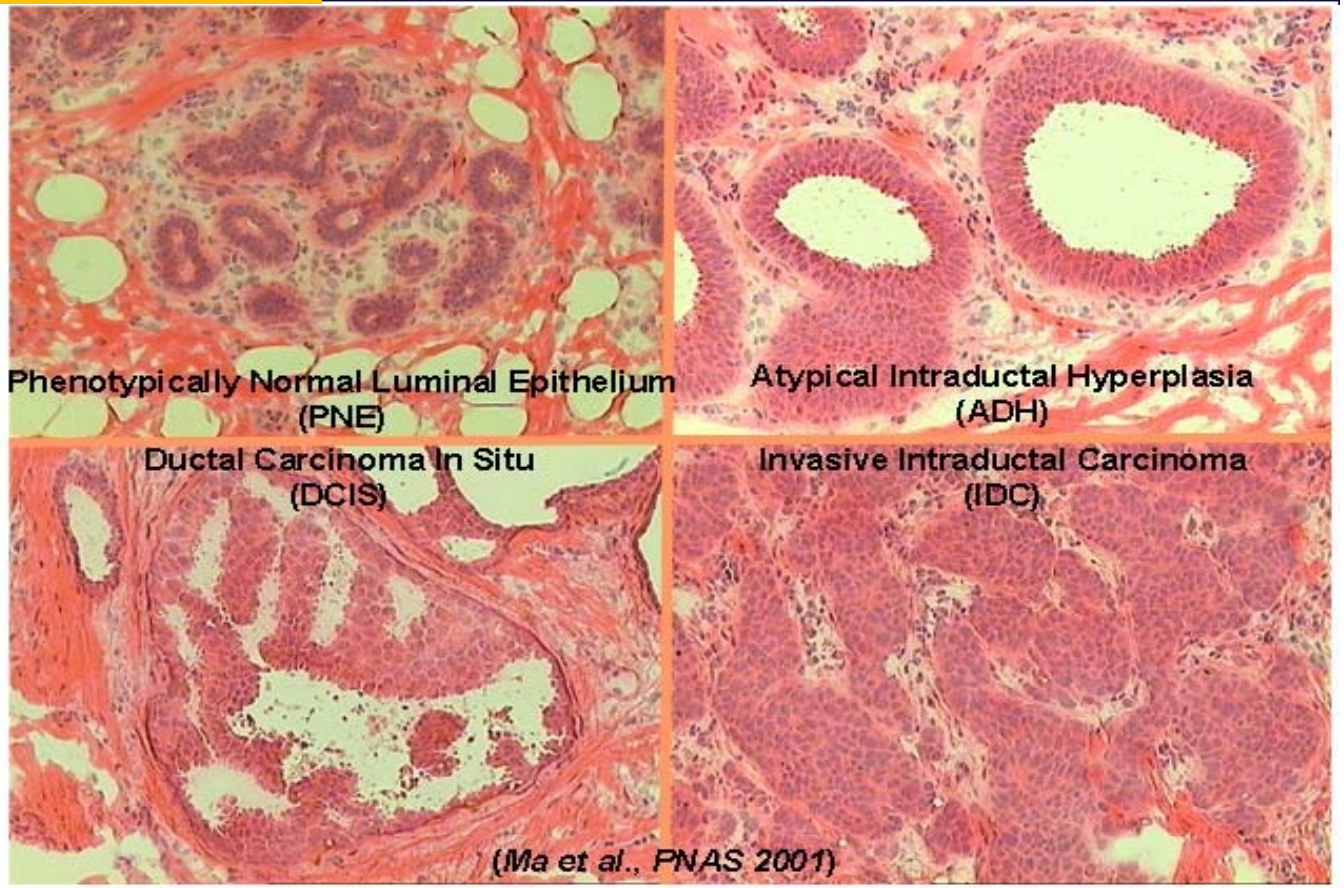
What is Cancer ?

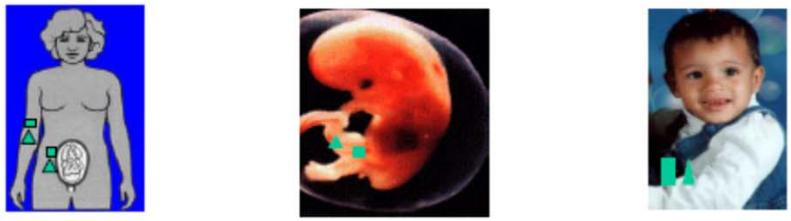
As I will try to demonstrate, it is now **possible to argue that cancer is rather an epigenetic disease**, which has **its roots (like many other chronic diseases** ... all of which are increasing worldwide) in **a disturbed epigenetic programming (of embryonic cells and / or stem cells) often at an early age (especially in the fetus) by an enormous amount of stressors and (epi)genotoxic factors** …



We intend **cancer as a tissue stem cells' disease**, in which many factors cooperate by **diverting the homeostatic mechanisms that regulate tissue repair and stem cell self-renewal,** due to **prolonged epi-genomic stress**

As for **cancers in infants**, we should point out that **at least the first stages of the malignant process are already present at the time of birth,** due to the **exposure of the embryo/phetus to an increasing number of stressors/pollutants**.

Exposures: PAHs, diesel particulates, environmental tobacco smoke, metals, pesticides, allergens



■ ▲ Biomarkers: e.g. exposure: blood or urinary levels of pesticides, PAHs, lead, mercury, genetic damage from PAH, immune changes, *gene or protein expression*; susceptibility: genetic variants and micronutrients

Developmental disorders, Cancer risk (chromosomal abnormalities), Asthma

The Telegraph

Science

Modern life is killing our children: Cancer rate in young people up 40 per cent in 16 years

By **Sarah Knapton**, SCIENCE EDITOR

3 SEPTEMBER 2016 • 9:30PM

New analysis of government statistics by researchers at the charity Children with Cancer UK found that there are now 1,300 more cancer cases a year compared with 1998, the first time all data sets were published.

Air pollution, obesity and a rise in electrical and magnetic fields is blamed for the surge in childhood cancer

"…the majority is probably caused by environmental factors.... obesity, pesticides and solvents inhaled during pregnancy, circadian rhythm disruption radiation from x-rays and CT scans, smoking during and after pregnancy, magnetic fields from power lines, **gadgets in homes**, and potentially, radiation from mobile phones.."

The importance of **(epi)genetic events *in utero*** has been suspected for many years, on the basis of the **correlation studies on twins with leukaemia**

http://www.telegraph.co.uk/science/2016/09/03/modern-life-is-killing-our-children-cancer-rate-in-young-people/

That **infant leukaemia may originate *in utero*** is also confirmed by the results of genetic studies that have found **translocations and gene sequences corresponding to the fusion genes later found in leukemic blasts, in blood samples (Guthrie cards) taken, at birth, from infants who subsequently would develop leukaemias..**

Today, **proleucemic translocations and clones are found in fetuses with a frequency much higher** than the incidence of leukemias

Early Human Development (2005) 81, 123–129

ELSEVIER

Early Human Development

www.elsevier.com/locate/earlhumdev

In utero origins of childhood leukaemia

Mel Greaves*

Abstract Chimaeric fusion genes derived by chromosome translocation are common molecular abnormalities in paediatric leukaemia and provide unique markers for the malignant clone. They have been especially informative in studies with twins concordant for leukaemia and in retrospective scrutiny of archived neonatal blood spots. These data have indicated that, in paediatric leukaemia, the majority of chromosome translocations arise in utero during foetal haemopoiesis. Chromosomal translocations and preleukaemic clones arise at a substantially higher frequency (~100×) before birth than the cumulative incidence or risk of disease, reflecting the requirement for complementary and secondary genetic events that occur postnatally. A consequence of the latter is a very variable and occasionally protracted postnatal latency of disease (1–15 years). These natural histories provide an important framework for consideration of key aetiological events in paediatric leukaemia.

.. the first unambiguous evidence for a **prenatal origin of leukaemia** was derived **from studies in identical twins with leukaemia**. A case of **identical (monozygotic) infant twins with leukaemia was recorded in 1882,** and, since that time, more than 70 pairs have been published albeit in variable detail ...

1

The **concordance** rate of leukaemia varies according to subtype and age.
For infants with ALL, the rate is exceedingly high (> 50%), for "COMMON" child-ALL, is ~10%.

2

Chromosomal translocations and preleukaemic clones arise at a substantially higher frequency (~100 X) before birth than the cumulative incidence or risk of disease.. reflecting the requirement for complementary and **secondary genetic events** that occur postnatally. A consequence of the latter is a very variable and occasionally protracted **postnatal latency** of disease (1—15 years).

3

Adult leukaemia (ALL/ AML), in contrast, has a **very low rate of concordance (< 1%).**

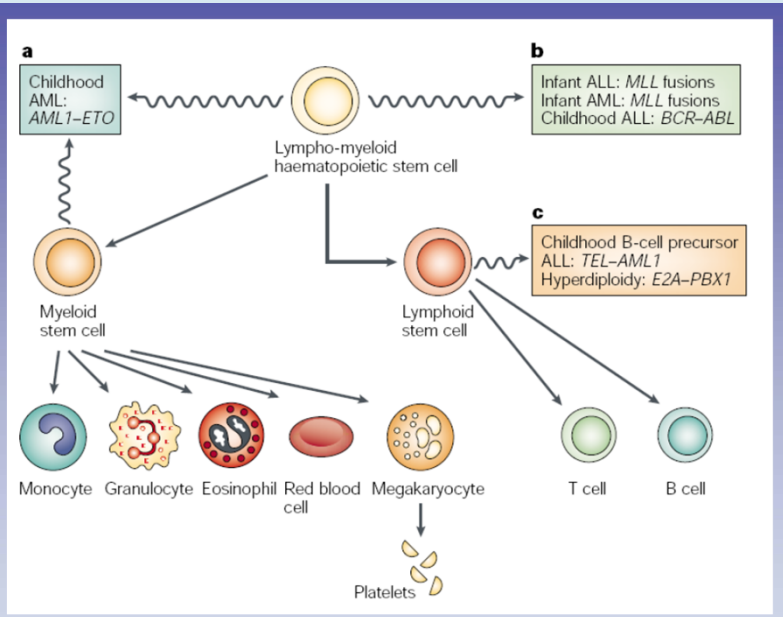
~1% of newborns had TEL-AML1 positive B lineage clones…
which represents **100 times** the incidence of **TEL-AML1 positive ALL (~1 in 12,000).**

Chromosome translocations can initiate leukaemogenesis, but are usually not sufficient, with additional postnatal events being required.

In childhood leukaemia, chromosome translocations arise mainly before birth during fetal haematopoiesis.

This is usually interpreted as the evidence that translocations are **stochastic genetic aberrations that** do not necessarily determine the onset of leukaemia, which would require additional genetic events during the postnatal period….

An **equally interesting interpretation** consists in assuming that, if less than 1% of children who have "produced" a translocation will develop leukaemia, it could be because **translocations are active genomic mutations, potentially adaptive to toxic exposures *in utero*..**



Different subtypes of leukaemia have distinctive chromosome translocations.

Translocations seem to arise at the level of haematopoietic stem cells, but their impact is cell-context dependent, resulting in different effects in different lineages.

Chromosome translocations are initiated by double-strand DNA breaks. The main repair mechanism underlying the resultant illegitimate recombination is probably non-homologous end-joining.

Nature Reviews Cancer **volume3**, pages639–649 (2003)

N Engl J Med 2008;359:722-34.

REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

Chromosomal Abnormalities in Cancer

Stefan Fröhling, M.D., and Hartmut Döhner, M.D.

CYTOGENETIC ABNORMALITIES ARE A CHARACTERISTIC ATTRIBUTE OF cancer cells. To date, clonal chromosome aberrations have been found in all major tumor types from more than 54,000 patients (http://cgap.nci.nih.gov/Chromosomes/Mitelman), and their identification continues as a result of technical improvements in conventional and molecular cytogenetics. The World Health Organization Classification of Tumours recognizes a growing number of such genetic changes and uses them to define specific disease entities. Many of these aberrations have emerged as prognostic and predictive markers in hematologic cancers and certain types of solid tumors. Furthermore, the molecular characterization of cytogenetic abnormalities has provided insights into the mechanisms of tumorigenesis and has, in a few instances, led to treatment that targets a specific genetic abnormality. This article discusses examples of two main classes of chromosomal abnormalities — balanced chromosomal rearrangements and chromosomal imbalances (Fig. 1 and 2) — with particular focus on their functional consequences and their implications (actual or potential) for the development of effective anticancer therapies.

Are *TRANSLOCATIONS* chromosomal aberrations or reactive/positive rearrangements ??

THE CAUSES OF **CHROMOSOMAL ABNORMALITIES** REMAINS POORLY UNDERSTOOD.

STUDIES OF VARIOUS TYPES OF LEUKEMIA HAVE SHOWN THAT CERTAIN ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES AND THERAPY WITH CYTOTOXIC DRUGS CAN INDUCE **CHROMOSOMAL ABERRATIONS**. FOR EXAMPLE, CASES OF MYELODYSPLASTIC SYNDROME OR AML THAT ARISE AFTER TREATMENT WITH *ALKYLATING AGENTS* ARE FREQUENTLY ASSOCIATED WITH UNBALANCED ABNORMALITIES, PRIMARILY DELETION OR LOSS OF CHROMOSOME 5 OR 7 (OR BOTH), WHEREAS **THERAPY WITH TOPOISOMERASE II INHIBITORS** IS TYPICALLY ASSOCIATED WITH BALANCED ABNORMALITIES, (**MOST COMMONLY TRANSLOCATIONS INVOLVING THE *MLL GENE ON CHROMOSOME* BAND 11Q23.1)**

OXFORD JOURNALS CONTACT US MY BASKET MY ACCOUNT

Carcinogenesis

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRENT ISSUE ARCHIVE SEARCH

Oxford Journals › Life Sciences › Carcinogenesis › Carcinogenesis Advance Access › 10.1093/carcin/bgl011

Exposure to **NHL-associated carcinogens**, such as **dioxin (in Seveso) or pesticides**, may cause **expansion of t(14;18)-positive clones.**

Carcinogenesis Advance Access first published online on March 16, 2006
This version published online on April 25, 2006
Carcinogenesis, doi:10.1093/carcin/bgl011

Published by Oxford University Press 2006
Received November 28, 2005
Revised February 11, 2006
Accepted March 7, 2006

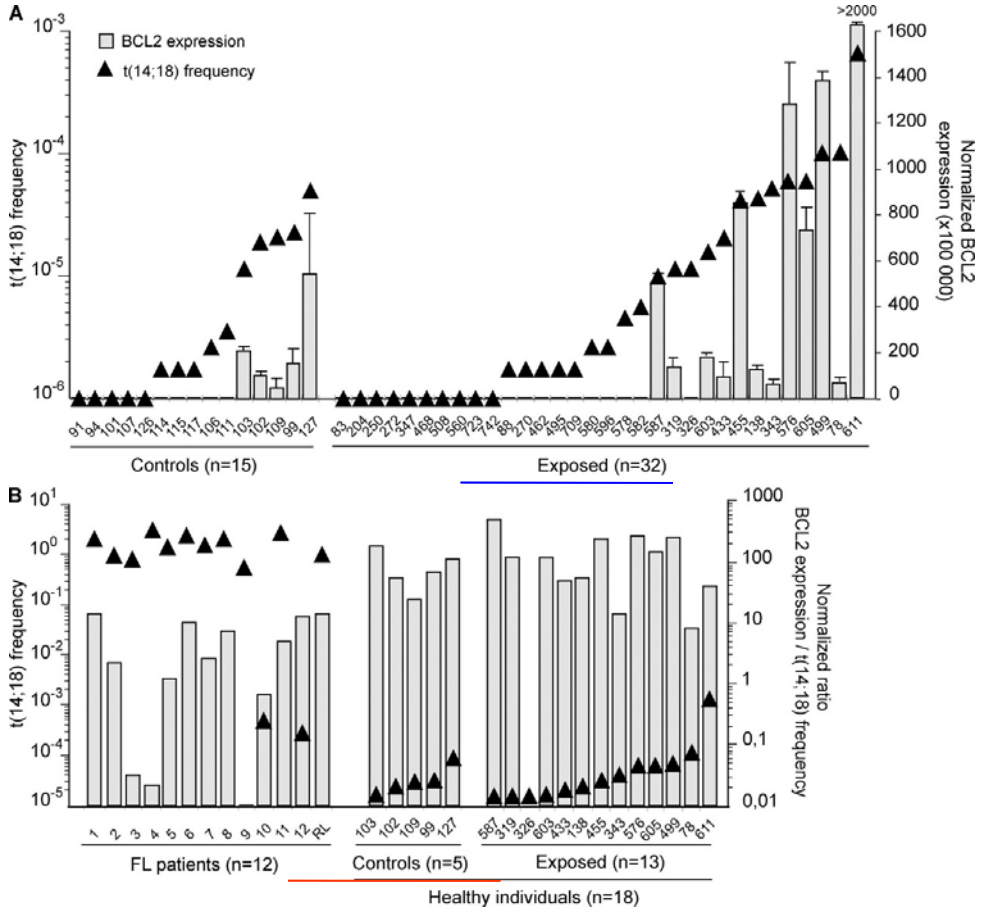
MOLECULAR EPIDEMIOLOGY AND CANCER PREVENTION

t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy

Andrea Baccarelli [1], Carsten Hirt [2], Angela C. Pesatori [1], Dario Consonni [1], Donald G. Patterson Jr. [3], Pier Alberto Bertazzi [1], Gottfried Dölken [4], and Maria Teresa Landi [5] *

JEM

Figure 2. t(14;18)+ cells in HI are actively transcribing BCL2 from the translocated allele



We can find exactly the **same (reactive) translocation** (++ expression of the **anti-apoptotic gene BCL-2**) in many **subjects chronically exposed to pesticides ..**

Agopian et al. Journal of Experimental Medicine 2009:206:1473-1483

Carcinogenesis vol.27 no.10 pp.2001–2007, 2006
doi:10.1093/carcin/bgl011
Advance Access publication March 16, 2006

t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy

Table III. Prevalence and frequency of t(14;18) translocations by plasma TCDD levels, zone of residence and diagnosis of chloracne

	t(14;18)-positive subjects		t(14;18) frequency[a]	
	%	(Positive/total)	Mean	(95% CI)
Plasma TCDD				
<10 p.p.t.	34.7	(25/72)	4.2[b]	(2.9–6.2)
10.0–475.0 p.p.t.	34.7	(25/72)	9.9[b]	(6.8–14.5)
Zone of residence at the time of the accident				
Reference	42.4	(14/33)	4.3[c]	(2.3–8.0)
R	26.9	(7/26)	4.9[c]	(2.2–10.7)
B	29.4	(10/34)	7.2[c]	(3.8–13.6)
A	37.3	(19/51)	9.3[c]	(5.8–14.8)
Chloracne after the accident				
No	35.2	(32/91)	6.2	(3.7–10.6)
Yes	34.0	(18/53)	6.7	(4.7–9.6)

[a]Geometric means and 95% CIs of the number of t(14;18) translocations/10^6 lymphocytes among t(14;18)-positive subjects, adjusted for age, smoking status (never, ex or current smoker) and smoking duration in multivariable analysis.
[b]$P = 0.006$, test for difference in mean t(14;18) frequency between plasma TCDD categories.
[c]$P = 0.04$, test for trend in mean t(14;18) frequency across residence zones.

Which obviously means that **it is not a question of stochastic mutations**.. or even simply **of damage caused by a single mutagenic agent (dioxin or pesticides)** ..

but rather of **specific and (re)active/adaptive molecular modifications induced by different stressors/pollutants**

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2004;351:250-9.

ORIGINAL ARTICLE

Lymphoma-Specific Genetic Aberrations in Microvascular Endothelial Cells in B-Cell Lymphomas

Berthold Streubel, M.D., Andreas Chott, M.D., Daniela Huber, Markus Exner, M.D., Ulrich Jäger, M.D., Oswald Wagner, M.D., and Ilse Schwarzinger, M.D.

BACKGROUND

The growth of most tumors depends on the formation of new blood vessels. In contrast to genetically unstable tumor cells, the endothelial cells of tumor vessels are considered to be normal diploid cells that do not acquire mutations.

RESULTS

We found that 15 to 85 percent (median, 37 percent) of the microvascular endothelial cells in the B-cell lymphomas harbored lymphoma-specific chromosomal translocations. In addition, numerical chromosomal aberrations were shared by the lymphoma cells and the endothelial cells.

CONCLUSIONS

Our findings suggest that microvascular endothelial cells in B-cell lymphomas are in part tumor-related and therefore reflect a novel aspect of tumor angiogenesis.

…. especially since we can find the same genetic and **chromosomal mutations, which are the consequence of complex molecular mechanisms** (the three proposed mechanisms of DNA breaks that can lead to translocations are **VDJ-Recombination, functional topoisomerase II or apoptotic endonucleases cleavage followed by gene fusions.**.) not only in the cells of the primary neoplastic clone (in this case, **lymphocytes**) but in **other cellular types... such as endothelial cells, which do not even have the same embryonic derivation**

Table 1. Cytogenetic Findings in 27 B-Cell Non-Hodgkin's Lymphomas and the Corresponding Tumor Endothelial Cells.*

Case No.	Diagnosis	Site	Patient's Age and Sex	Cytogenetic Aberrations		Endothelial-Cell Markers	Endothelial Cells with Genetic Aberrations
				In Lymphoma Cells (Stem-Cell Line)	In Endothelial Cells		
							%
1	FL 1†	Lymph node	55 yr, M	49,XY,+X,+11,t(14;18)(q32;q21),+21	t(14;18)(q32;q21), +X,+11,+21	CD31, WF	21
2	FL 3†	Lymph node	43 yr, M	53,XY,+2,+3,+7,+7,+8,+11,+12, t(14;18)(q32;q21)	t(14;18)(q32;q21), +2,+3,+7,+7,+8,+11,+12	CD31, UEL	32
3	FL 2†	Lymph node	61 yr, F	49,XX,+X,+5,der(5)t(1;5)(q11;q31), +i(6)(p10),t(14;18)(q32;q21)	t(14;18)(q32;q21),+X,+5	CD31, WF	28
4	FL 2†	Lymph node	83 yr, F	47,XX,+7,t(14;18)(q32;q21)	t(14;18)(q32;q21),+7	CD31, CD34	29
5	FL 1†‡	Lymph node	32 yr, M	46,XY,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, WF, UEL, CD34	80
6	FL 3	Lymph node	60 yr, F	t(14;18)(q32;q21)(IGH con BCL2×2)	t(14;18)(q32;q21)	CD31, WF, UEL, CD34	53
7	FL 1†	Lymph node	48 yr, M	46,XY,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, UEL	48
8	FL 1†	Lymph node	54 yr, F	49,XX,t(1;X)(q43;q24), +2,der(4)t(4;12)(p15;q13),del(6)(q21),+7, dup(9)(q21q32),+13,t(14;18)(q32;q21)	t(14;18)(q32; q21),+2,+7,+13	CD31, WF	50
9	FL 1†	Lymph node	39 yr, F	46,XX,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, WF	63
10	FL 1†	Lymph node	40 yr, M	46,XY,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, CD34	27
11	FL 1†	Lymph node	46 yr, M	46,XY,t(14;18)(q32;q21),del(13)(q12q31)	t(14;18)(q32;q21), del(13)(q14)(RB1×1)	CD31, WF, UEL, CD34	18
12	FL 1†	Lymph node	60 yr, F	48,XX,+5,+5,t(14;18)(q32;q21)	t(14;18)(q32;q21),+5,+5	CD31, WF, UEL, CD34	21

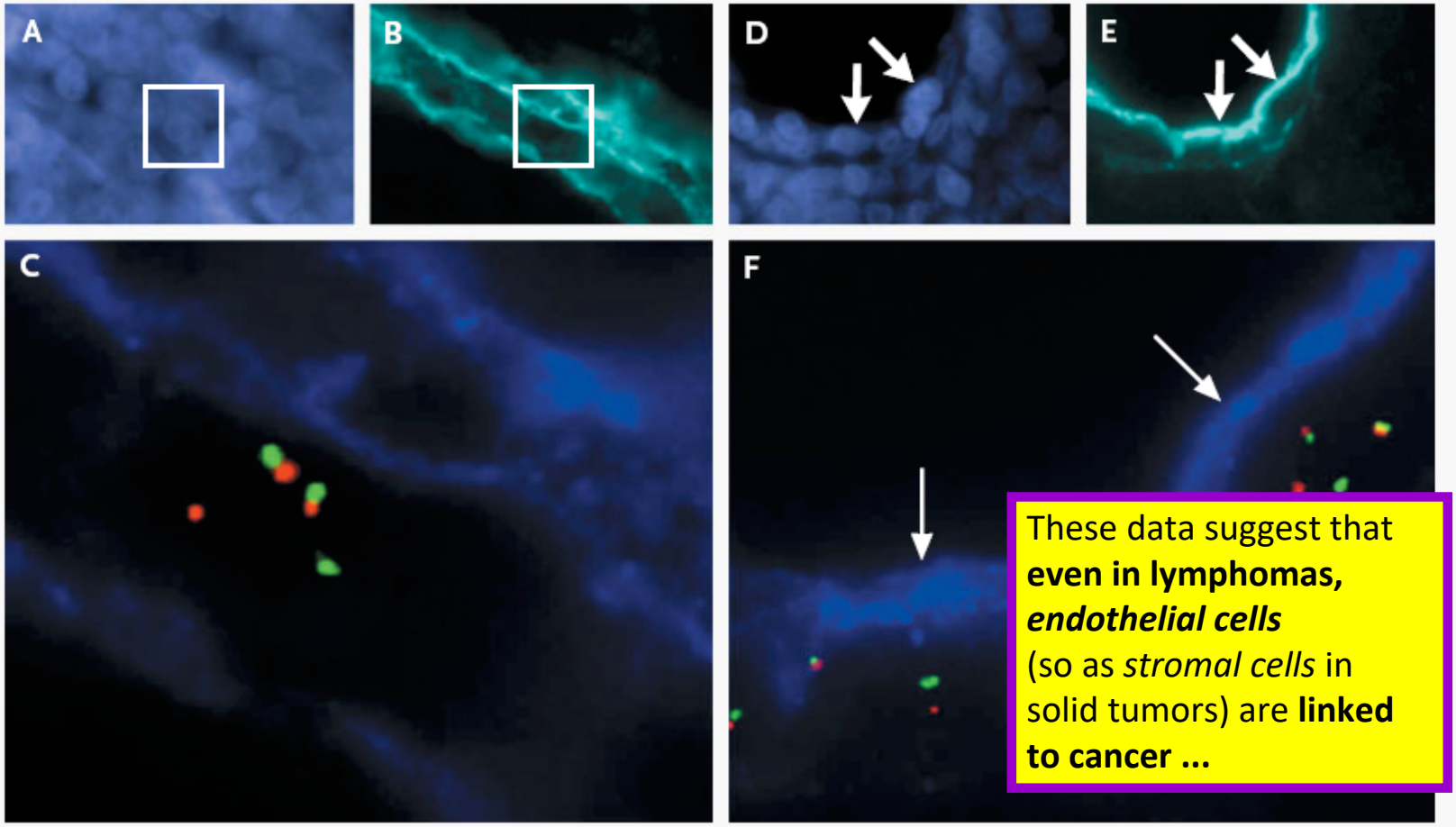
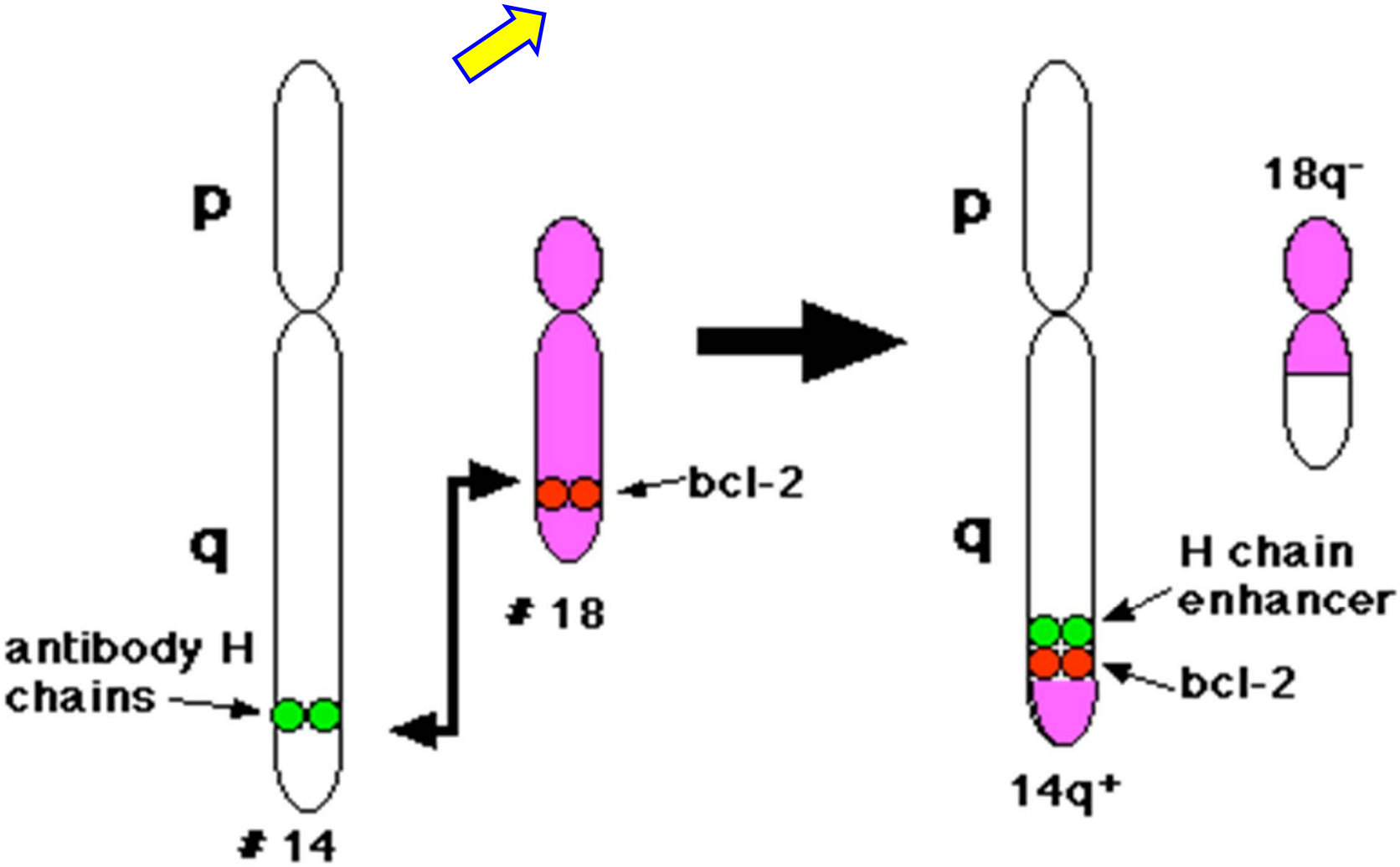


Figure 2. *IGH* Translocations in Endothelial Cells in Follicular Lymphoma and Mantle-Cell Lymphoma.

In a follicular lymphoma (Case 11), the nucleus of an endothelial cell (Panel A, box) that is labeled with the use of anti–von Willebrand factor antibody (Panel B, box) reveals two fusion signals for the green *IGH* probe and the red *BCL2* probe (Panel C), indicating t(14;18)(q32;q21). In a mantle-cell lymphoma (Case 20), arrows indicate nuclei that belong to the endothelial cells of a cross-sectioned vessel (Panel D) with staining for CD34 (Panel E). Two CD34+ endothelial cells (Panel F, arrows) show two and three fusion signals for t(11;14)(q13;q32), respectively.

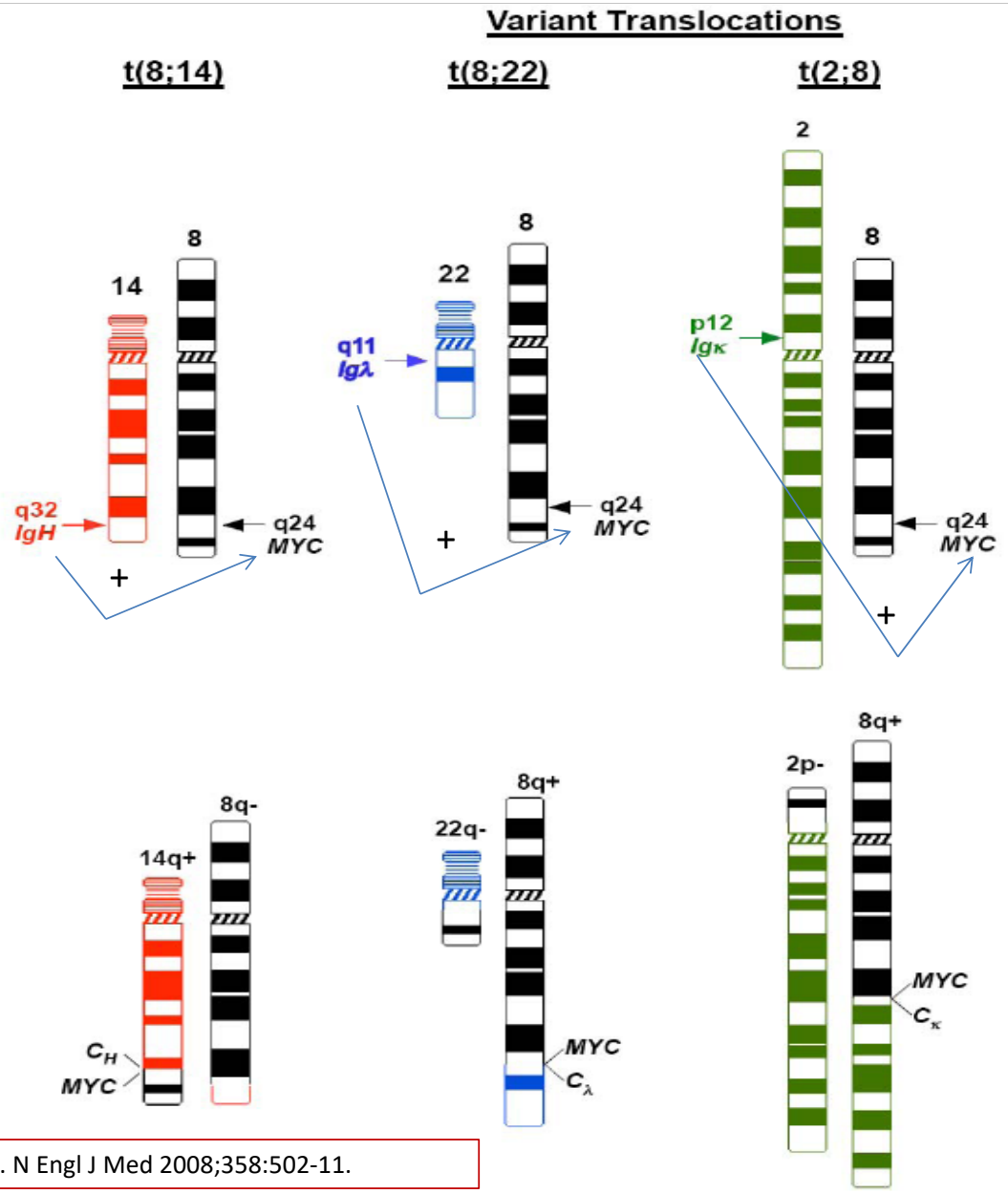
But the **most significant evidence of the non-stochastic, but reactive and, so to speak, teleonomic character of neoplastic translocations** comes from the molecular analysis: in this case, for example, **an anti-apoptotic gene is exposed to the immunoglobulin enhancer to determine the immortalization of cells** !!

IN THE CANCEROUS B CELLS, THE PORTION OF CHROMOSOME 18 CONTAINING THE *BCL-2* LOCUS HAS UNDERGONE A **RECIPROCAL TRANSLOCATION WITH THE PORTION OF CHROMOSOME 14 CONTAINING THE ANTIBODY HEAVY CHAIN LOCUS**. **THIS T(14;18) TRANSLOCATION PLACES THE *BCL-2* GENE CLOSE TO THE HEAVY CHAIN GENE *ENHANCER*.**



H Chain-enhancer is very active in B cells...

Even more interesting is **the mechanism, (quite similar) that occurs in *Burkitt's lymphoma*** (in particular in the areas of Africa infested by *Anopheles / Plasmodium falciparum* and *EBV*) with 3 forms of translocations determining the **exposure of another oncogene (c-MYC) to the enhancer sequences of Ig or T-lymphocyte receptors** ..



THE FIRST EVIDENCE THAT CANCER ARISES FROM SOMATIC GENETIC ALTERATIONS CAME FROM STUDIES OF **BURKITT'S LYMPHOMA**, IN WHICH ONE OF **THREE DIFFERENT TRANSLOCATIONS** JUXTAPOSES AN **ONCOGENE, *MYC*, ON CHROMOSOME 8q24** TO ONE OF THE **LOCI FOR IMMUNOGLOBULIN GENES**. CHROMOSOMES **14q, 22q, AND 2q — THE TRANSLOCATION PARTNERS — EACH CARRIES ENHANCER ELEMENTS IN THE IMMUNOGLOBULIN LOCI, THEREBY ACTIVATING THE JUXTAPOSED *C-MYC ONCOGENE***

Are the ***antibody gene loci*** **quite *"dangerous places"* for *proto-oncogenes*** to take up residence ?

Croce CM. **Oncogenes and Cancer**. N Engl J Med 2008;358:502-11.

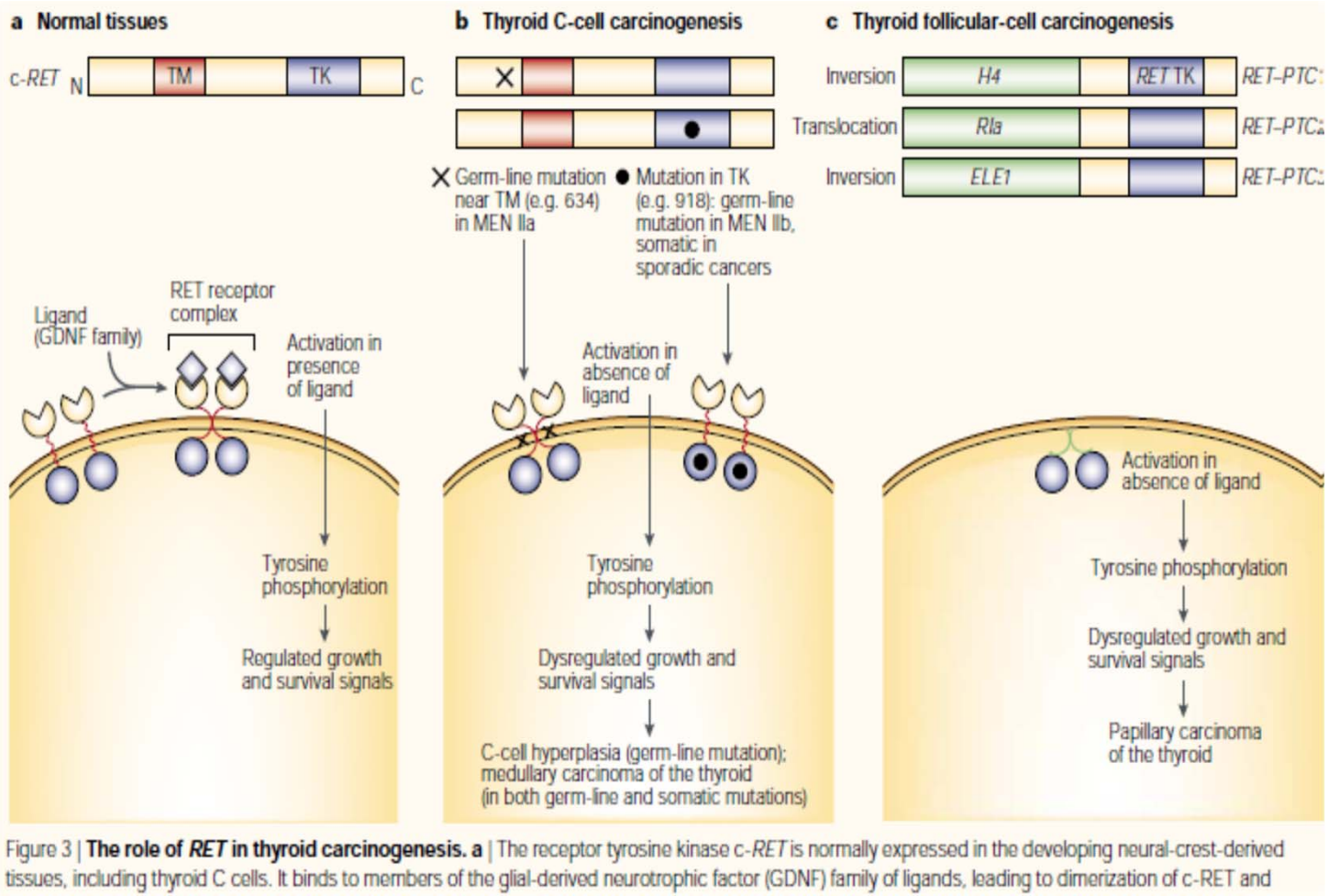
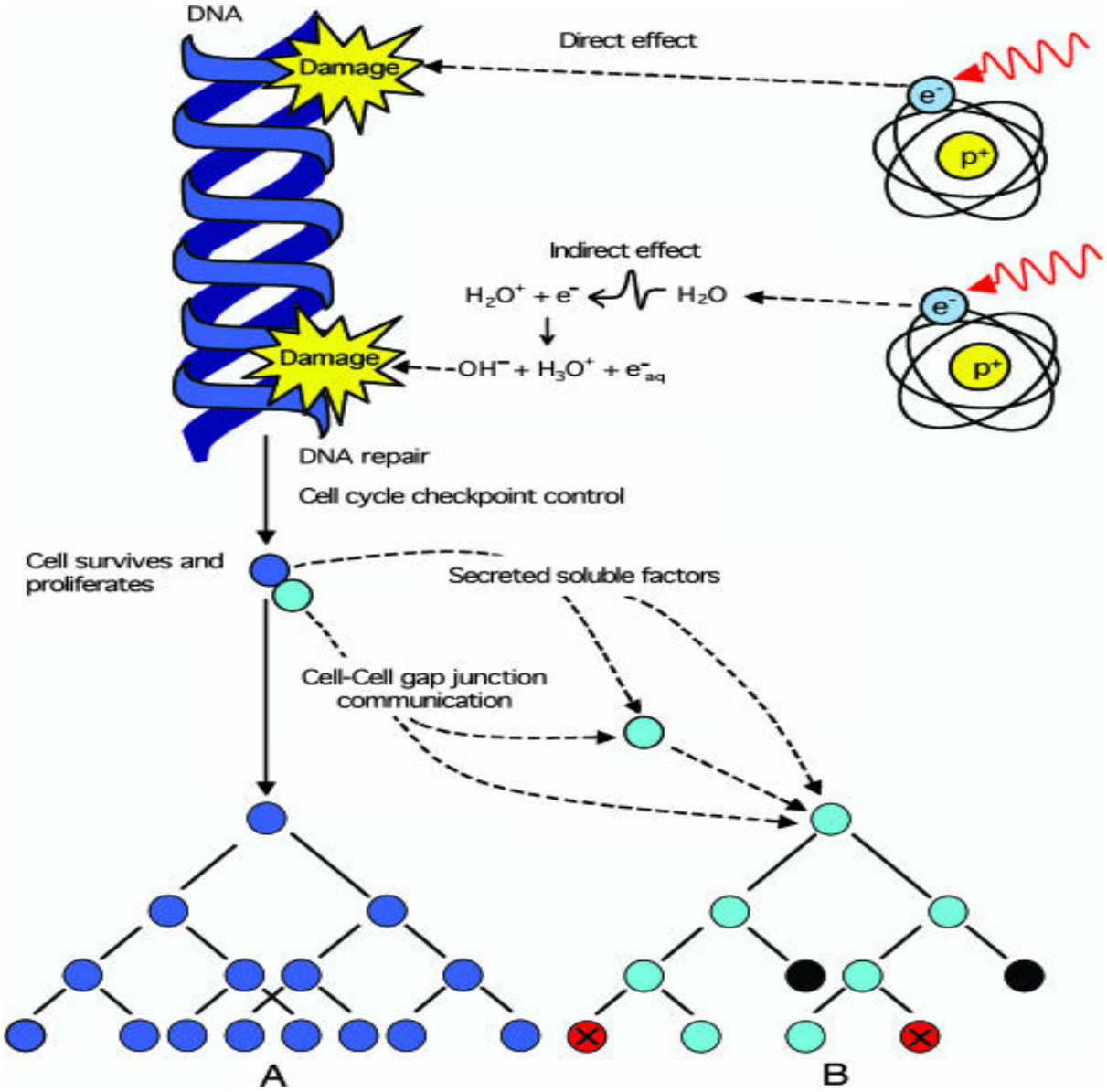


Figure 3 | **The role of *RET* in thyroid carcinogenesis. a** | The receptor tyrosine kinase c-*RET* is normally expressed in the developing neural-crest-derived tissues, including thyroid C cells. It binds to members of the glial-derived neurotrophic factor (GDNF) family of ligands, leading to dimerization of c-RET and

.. or in the areas of **Chernobyl, where the oncogene C-RET, involved in the development of the thyroid gland/cancer**, is recurrently translocating (especially **in the children of the exposed to radiations**) ....
(In Belarus, the incidence of **thyroid cancer was multiplied by 30** in 1995 and **by 100 in the regions closest to Chernobyl**)..

Il *secondo pilastro* della radiobiologia classica scaturì dalla **definizione più precisa del danno al DNA**, che seguì alla descrizione, nel **1961**, di **rotture *stocastiche*** di **uno o di entrambi i filamenti della doppia elica** (*Single Strand Breaks-SSBs; Double Strand Breaks-DSBs*), nel DNA esposto a radiazioni. Su queste basi nel **1973** venne formulata **l'*equazione lineare quadratica*** *(Linear Quadratic equation-lq)* fondata **sulla tesi che *basse dosi* di radiazioni causano essenzialmente *SBSs*, facilmente riparabili,** mentre ad ***alte dosi* predominano le rotture, «potenzialmente letali» per la cellula, di entrambi i filamenti** della doppia elica …

Soltanto un'*esposizione massiva* (dell'ordine di 1-2 o più Gy) a radiazioni provocherebbe **danni significativi ai tessuti e alla salute umana …** piuttosto astrattamente, suddivisi in: «***deterministici***» (da danno cellulare diretto) e appunto «***stocastici***» (da danno al DNA).



International Journal of Environmental Research and Public Health

Int J Environ Res Public Health. 2018 Sep 10;15(9).

MDPI

Review

Ionizing Radiation and Human Health: Reviewing Models of Exposure and Mechanisms of Cellular Damage. An Epigenetic Perspective

Ernesto Burgio [1,2,*], Prisco Piscitelli [2] and Lucia Migliore [3]

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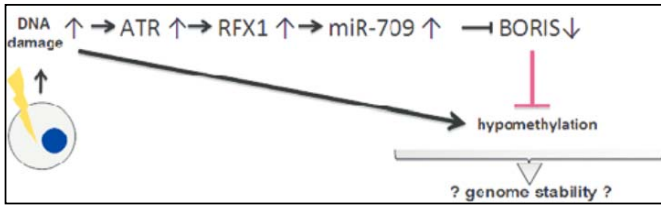
2 Euro Mediterranean Scientific Biomedical Institute-ISBEM Research Centre, 72023 Mesagne (Brindisi), Italy; priscofreedom@hotmail.com
3 Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, 56126 Pisa, Italy; lucia.migliore@med.unipi.it
* Correspondence: erburg@libero.it; Tel.: +39-0831-713511

Even as regards the **effects of ionizing radiation, SMT model appears obsolete**: we have just published a review to show how, also in this case, there are **no stochastic/mechanical lesions due to the energy connected to radiation, but reactive DSBs and complex potentially adaptive/defensive genomic modifications** (including trans*l*ocations)



The available evidence makes this classical model increasingly less acceptable, because the exposure to low doses of IR seems to have **carcinogenic effects, even after years or decades, both in the exposed individuals and in subsequent generations**. In addition, **the cells that survived the exposure to low doses, despite being apparently normal, accumulate damages that become evident in their progeny, such as nonclonal chromosomal aberrations, which can be found even in cells not directly irradiated due to the exchange of molecular signals and complex tissue reactions** involving neighboring or distant cells. ..For all these reasons, a paradigm shift is needed..

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Pathophysiology 16 (2009) 71–78

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www.elsevier.com/locate/pathophys

Electromagnetic fields stress living cells

Martin Blank [a,*], Reba Goodman [b]

[a] *Department of Physiology, Columbia University, New York, NY, USA*
[b] *Department of Pathology, Columbia University, New York, NY, USA*

Received 30 January 2009; accepted 30 January 2009

Abstract

Electromagnetic fields (EMF), in both ELF (extremely low frequency) and radio frequency (RF) ranges, activate the cellular stress response, a protective mechanism that induces the expression of stress response genes, e.g., HSP70, and increased levels of stress proteins, e.g., hsp70. The 20 different stress protein families are evolutionarily conserved and act as 'chaperones' in the cell when they 'help' repair and refold damaged proteins and transport them across cell membranes. Induction of the stress response involves activation of DNA, and despite the large difference in energy between ELF and RF, the same cellular pathways respond in both frequency ranges. Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF, and studies with model biochemical systems suggest that EMF could interact directly with electrons in DNA. While low energy EMF interacts with DNA to induce the stress response, increasing EMF energy in the RF range can lead to breaks in DNA strands. It is clear that in order to protect living cells, EMF safety limits must be changed from the current thermal standard, based on energy, to one based on biological responses that occur long before the threshold for thermal changes.

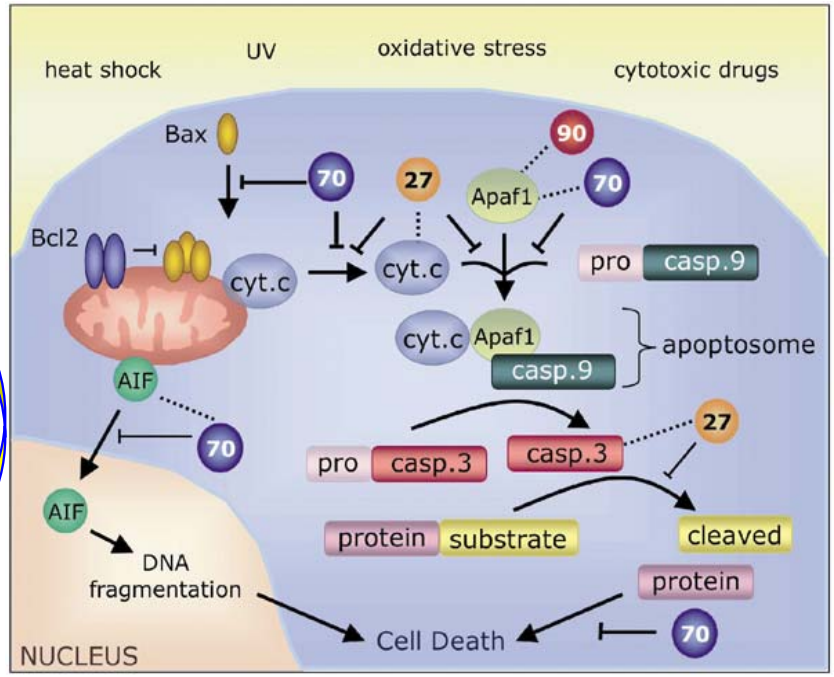
DANGER SIGNALS !

… it is important to realize that **the stress response occurs in reaction to a potentially harmful environmental influence.** The stress response **is an unambiguous indication that cells react to EMF as potentially harmful**. It is therefore **an indication of compromised cell safety, given by the cell, in the language of the cell**.

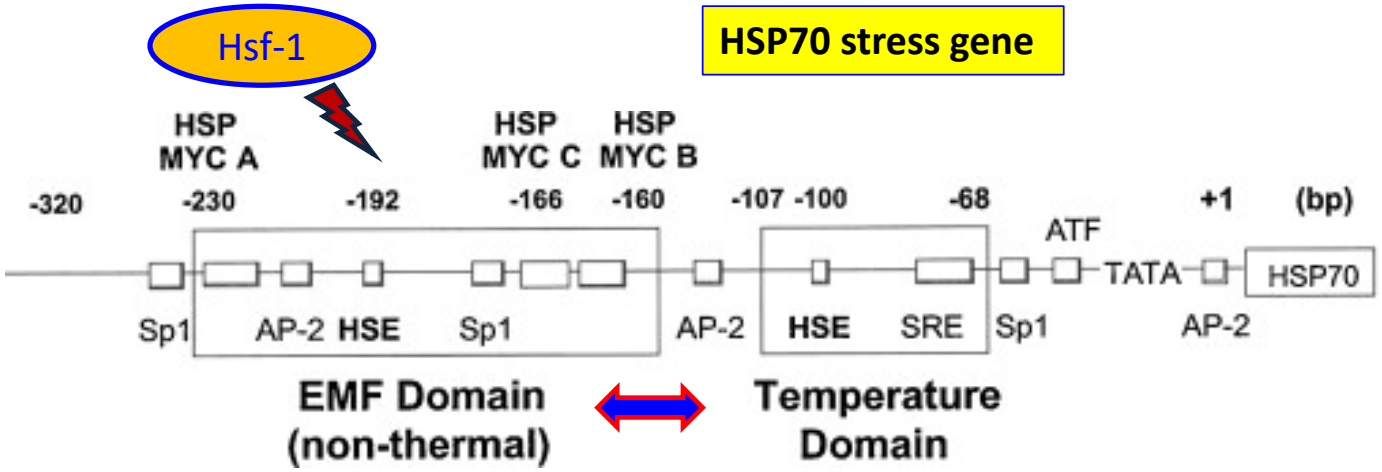
The **low threshold level of the stress response shows that the current safety standards are much too high to be considered safe.**

The **relatively low field strengths that can affect biochemical reactions** is a further indication that **cells are able to sense potential danger long before there is an increase in temperature …** the **thermal standard used by agencies to measure safety is at best incomplete, and in reality not protective …**
Non-thermal ELF mechanisms are as effective as thermal RF mechanisms in **stimulating the stress response** and other protective mechanisms.

Finally, **since both ELF and RF activate the same biology, simultaneous exposure to both is probably additive** and… **total EMF exposure is important…**



Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF...



Synthesis of this stress protein is initiated in a **region of the promoter** where a transcription factor known as **Heat Shock Factor 1 (HSF-1) binds to a Heat Shock Element (HSE).**
The **EMF sensitive region on HSP70 promoter** is **upstream from the thermal domain of the promoter and is not sensitive to increased temperature**. The binding of **HSF-1** to **HSE** occurs at **–192** in the **HSP70 promoter** relative to the transcription initiation site.

The **EMF domain contains three nCTCTn myc-binding sites –230, –166 and –160 relative to the transcription initiation site and upstream of the binding sites for the heat shock (nGAAn)** and serum responsive elements…. **The electromagnetic response elements (EMREs) have also been identified on the c-*myc* promoter and are also responsive to EMF**

Pathophysiology
Volume 16, Issues 2-3, August 2009, Pages 71-78

Sci Rep. 2019 Feb 4;9(1):1333. doi: 10.1038/s41598-018-37372-2.

www.nature.com/scientificreports

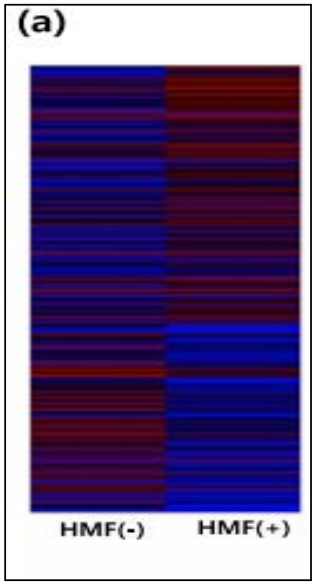
SCIENTIFIC REPORTS

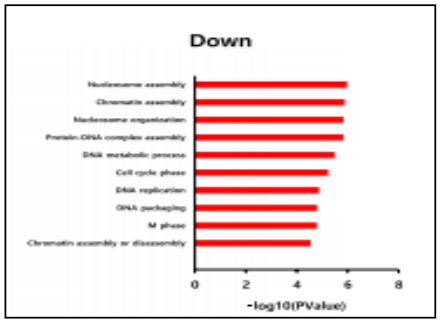
Published online: 04 February 2019

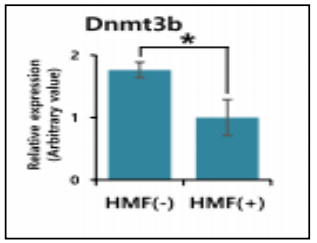
Effects of a hypomagnetic field on DNA methylation during the differentiation of embryonic stem cells

Soonbong Baek[1], Hwan Choi[1], Hanseul Park[1], Byunguk Cho[1], Siyoung Kim[1] & Jongpil Kim[1,2]

It has been reported that hypomagnetic fields (HMFs) have a negative influence on mammalian physiological functions. We previously reported that HMFs were detrimental to cell fate changes during reprogramming into pluripotency. These studies led us to investigate whether HMFs affect cell fate determination during direct differentiation. Here, we found that an HMF environment attenuates differentiation capacity and is detrimental to cell fate changes during the *in vitro* differentiation of embryonic stem cells (ESCs). Moreover, HMF conditions cause abnormal DNA methylation through the dysregulation of DNA methyltransferase3b (Dnmt3b) expression, eventually resulting in incomplete DNA methylation during differentiation. Taken together, these results suggest that an appropriate electromagnetic field (EMF) environment may be essential for favorable epigenetic remodeling during cell fate determination via differentiation.







…campi ipomagnetici (HMF) influenzano la determinazione del destino cellulare…
interferendo sulla **differenziazione in vitro delle cellule staminali embrionali (ESC).**
…attraverso la **disregolazione dell'espressione di *DNA metiltransferasi 3b (Dnmt3b),***
con conseguente **metilazione incompleta del DNA**

SCIENCE ADVANCES | RESEARCH ARTICLE

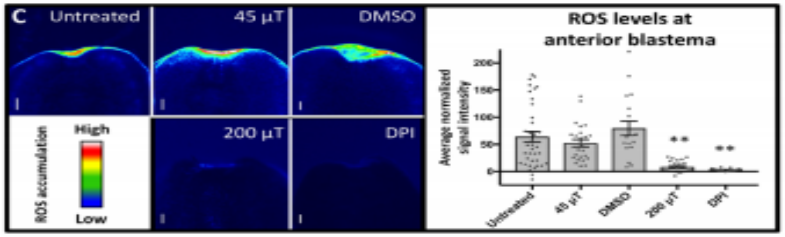
Sci Adv. 2019 Jan 30;5(1):eaau7201. doi: 10.1126/sciadv.aau7201.

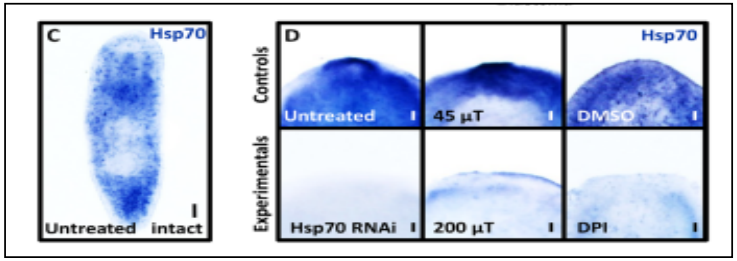
BIOPHYSICS

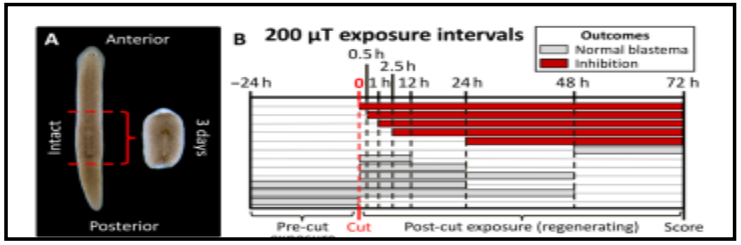
Weak magnetic fields alter stem cell–mediated growth

Alanna V. Van Huizen[1], Jacob M. Morton[1], Luke J. Kinsey[1], Donald G. Von Kannon[1], Marwa A. Saad[1], Taylor R. Birkholz[1], Jordan M. Czajka[1], Julian Cyrus[2], Frank S. Barnes[2], Wendy S. Beane[1]*

Biological systems are constantly exposed to electromagnetic fields (EMFs) in the form of natural geomagnetic fields and EMFs emitted from technology. While strong magnetic fields are known to change chemical reaction rates and free radical concentrations, the debate remains about whether static weak magnetic fields (WMFs; <1 mT) also produce biological effects. Using the planarian regeneration model, we show that WMFs altered stem cell proliferation and subsequent differentiation via changes in reactive oxygen species (ROS) accumulation and downstream heat shock protein 70 (Hsp70) expression. These data reveal that on the basis of field strength, WMF exposure can increase or decrease new tissue formation in vivo, suggesting WMFs as a potential therapeutic tool to manipulate mitotic activity.







Campi magnetici statici deboli (WMF <1 mT) producono **alterazioni della proliferazione delle cellule staminali e della successiva differenziazione** attraverso cambiamenti nell'**accumulo di specie reattive dell'ossigeno (ROS)** e nell'**espressione della proteina di shock termico 70 (Hsp70)**.

Questi dati rivelano che sulla base della forza del campo, l'esposizione al WMF può aumentare o diminuire la **formazione di nuovo tessuto *in vivo*...**

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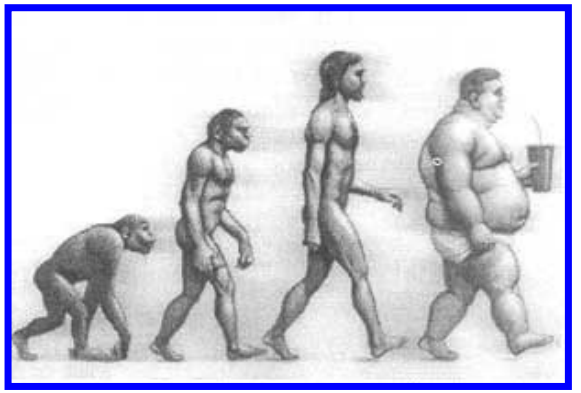
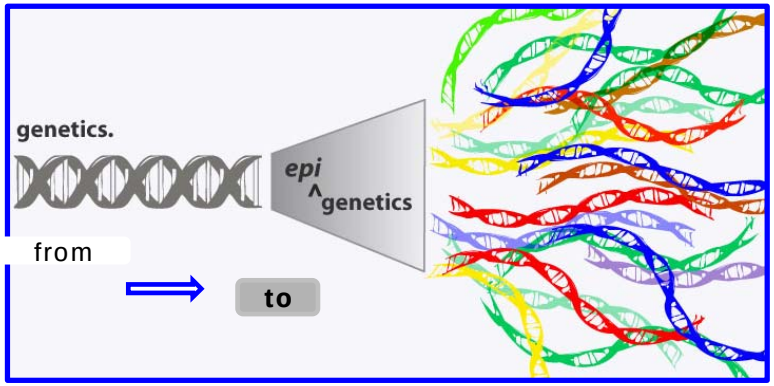


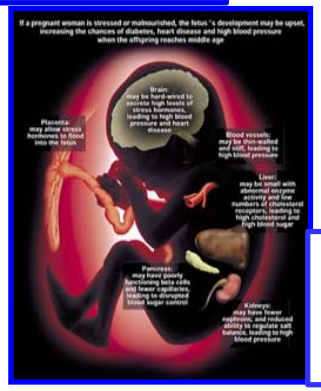
This one was the slide by which I had started my talk two years ago at the I Congress ..
I would like to conclude now by **briefly re-connecting to the reflections of those days…**

Evolution of DOHaD: the impact of environmental hazards on the origins of current "pandemics"



ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute

ECERI
European Cancer and Environment Research Institute



It has been well known for many years that **prenatal life is not fully protected** in the uterine microenvironment. **But only over the last decade** we have been focusing on mechanisms and modalities of **maternal and foetal exposure** to an impressive range of chemicals (eg .: endocrine disruptors) , physical factors (eg .:EMFs) and biological agents (eg .: viruses) **able to induce potentially adaptive and predictive epigenetic changes in the embryo-fetal genome, thus interfering with the programming of tissues and organs in an often irreversible way.**

CHEMICAL FALL OUT

ENDOCRINE DISRUPTORS 1

2 **HEAVY METALS**

3 **ULTRAFINE PARTICLES**

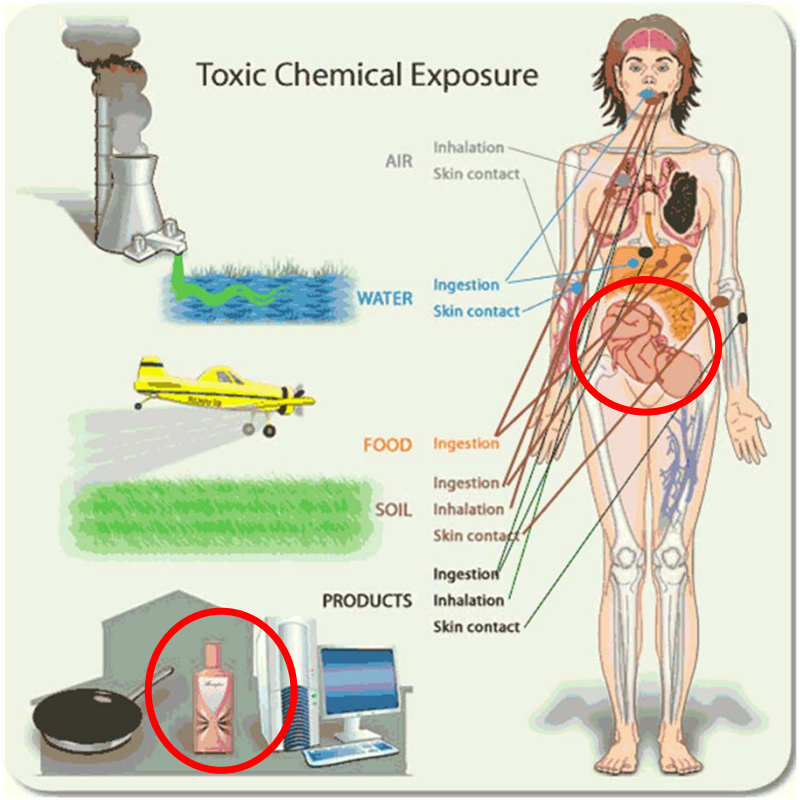
The gift our mothers never wanted to give us

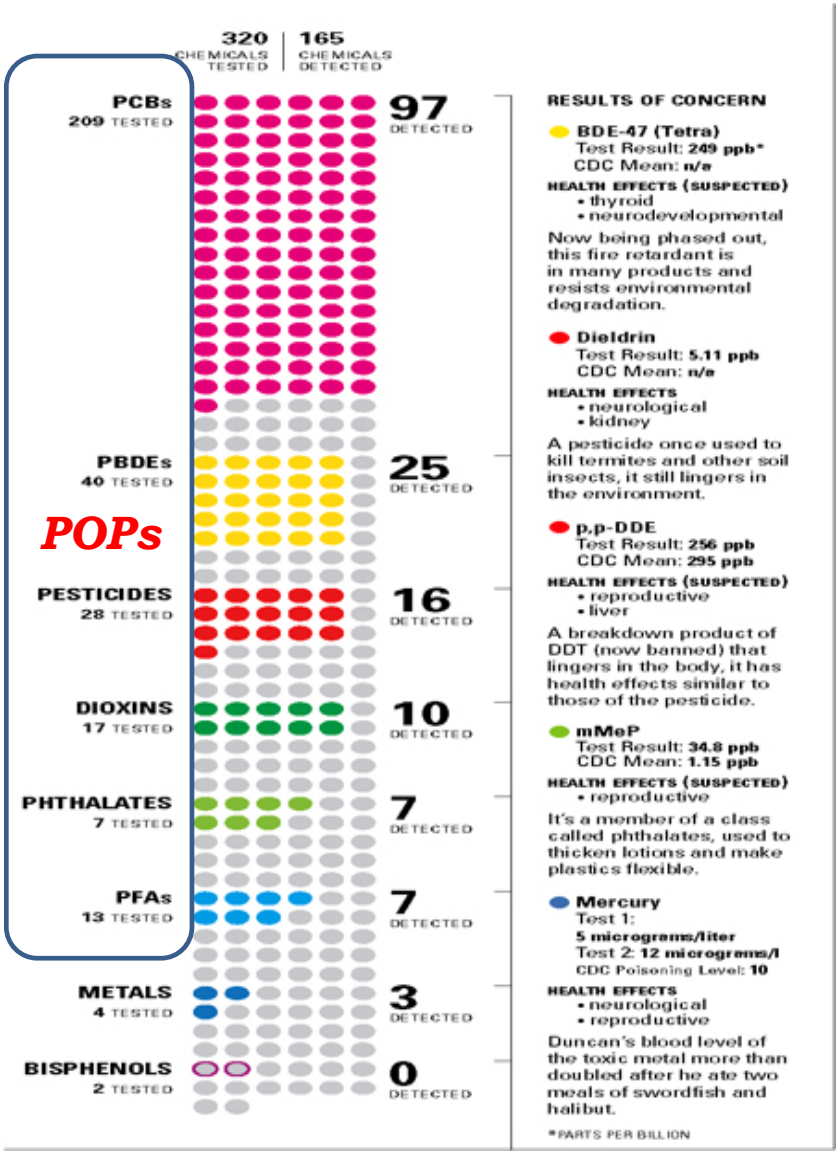
http://www.ewg.org/reports/generations/

.. at present many studies, in various parts of the world, are evaluating the **global chemical body burden .. especially in women, embryos/fetuses and children, providing dramatic results**.

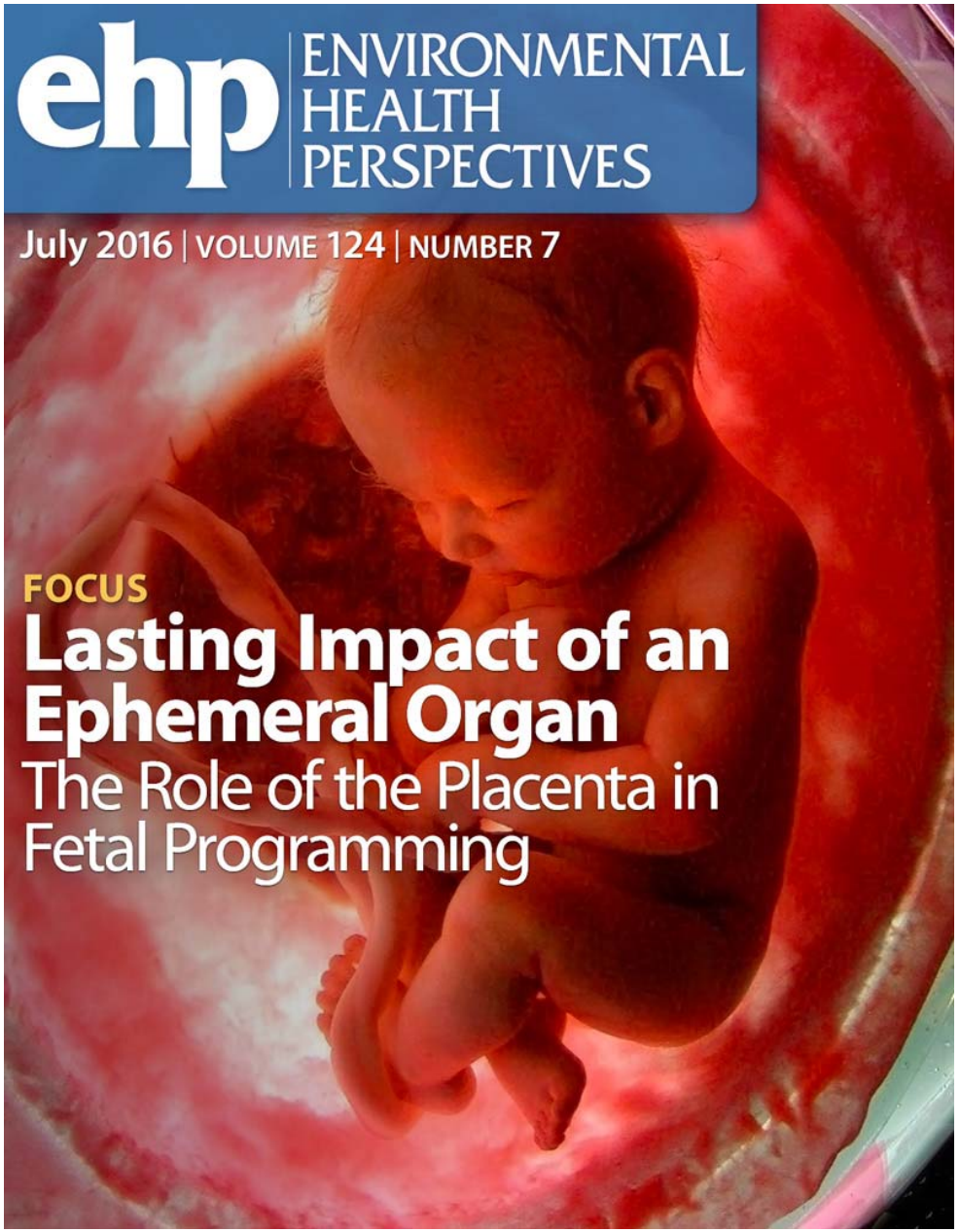
Monitoring Body-Burdens

> 700 different synthetic chemicals or heavy metals found in cord blood..





In this context, the organ that acquires a **truly extraordinary importance is the PLACENTA**: an organ that has been little studied until a few years ago and **that emerges as a sort of "black box" for programming (epigenetically)** the different **fetal tissues and organs**



Published in final edited form as:

Am J Obstet Gynecol. 2015 October ; 213(4 0): S14–S20. doi:10.1016/j.ajog.2015.08.030.

THE PLACENTA IS THE CENTER OF THE CHRONIC DISEASE UNIVERSE

Kent L. Thornburg[1,2,3] and **Nicole Marshall**[2,3]

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[2]Knight Cardiovascular Institute, Center for Developmental Health, School of Medicine, Oregon Health & Science University Portland, Oregon 97239

[3]Department of Obstetrics & Gynecology, Oregon Health & Science University Portland, Oregon 97239

Abstract

Over the past quarter century it has become clear that adult onset chronic diseases like heart

PROGRAMMA CCM 2017– PROGETTI ESECUTIVI IN ORDINE DECRESCENTE DI PUNTEGGIO DI VALUTAZIONE				
N.	**TITOLO**	**ENTE PARTNER**	**ID**	**IMPORTO**
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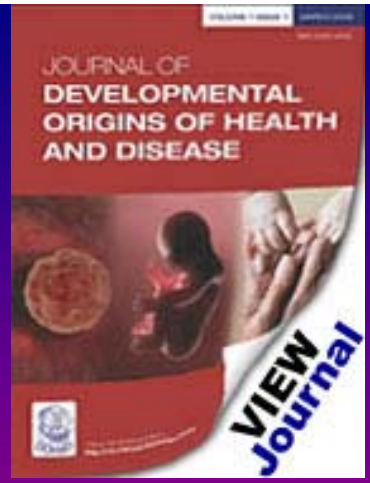
2	SCEGLIERE LE PRIORITÀ DI SALUTE E SELEZIONARE GLI INTERVENTI EFFICACI PER PREVENIRE IL CARICO DELLE MALATTIE CRONICHE NON TRASMISSIBILI	PIEMONTE	6	€ 449.250,00
3	SVILUPPO E VALIDAZIONE DI UN SISTEMA DI MONITORAGGIO EPIDEMIOLOGICO DELLE DEMENZE BASATO SUI DATI DEI SISTEMI INFORMATIVI SANITARI	CAMPANIA	5	€ 450.000,00
4	AMBIENTE, PROGRAMMAZIONE EPIGENETICA FETALE E PREVENZIONE DELLE PATOLOGIE CRONICHE	SARDEGNA	9	€ 448.000,00

We recently received a first **funding from the Italian Ministry of Health to study hundreds of placentas,** particularly in highly polluted areas such as the city of **Taranto, exposed to the largest Italian steel plant (ILVA)**

Mass spectrometry (IZS Bologna)
Immunohistochemistry (University of Cagliari)
Epigenetics (University of Pisa)
Mitochondria (University of Milan)
Metabolomics (University of Cagliari)
Follow-up of children (FIMP - Federazione Medici Pediatri) --> early diagnosis and personalized treatment

Eventually, during the last years, the ***fetal programming mismatch theory*** has been transformed **from a theory essentially useful to explain the pathogenic mechanisms causing certain diseases of adulthood, into the key-model theory of the embryo-fetal origins of adult diseases (DOHA-Developmental Origins of Health and Diseases)**



Obesogens

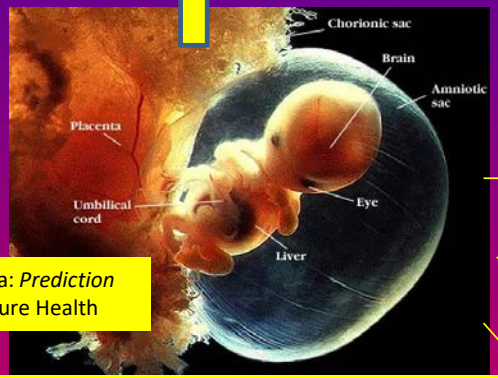
Multiorgan Effects of Endocrine Disruptors

Pesticides

In Vitro Fertilization

Materno Fetal Stress

Obesity/Metabolic Syndrome/Diabetes 2



Placenta: *Prediction* of Future Health

Developmental Time Windows of Vulnerability

Cardiovascular Diseases

Ipertension

Asthma and allergies

Lung Development ⇓

Reproductive Diseases/Dysfunctions

Semen Abnormalities

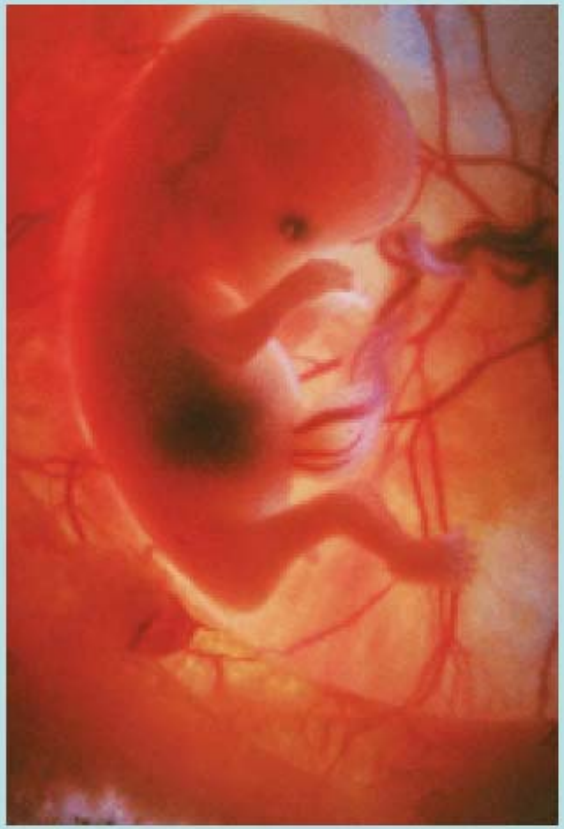
CANCER

Neurobehavioral Deficits and Diseases

Psychiatric Diseases

DOHAD

Developmental Programming



Exposure of developing tissues or organs to an adverse stimulus or insult during critical periods of development that can permanently reprogram normal physiological responses in such a way as to give rise to disease later in life

According to such a dynamic model, ***Infant leukaemias,*** **which have registered the highest increase,** could be considered an **evolutionary process gone awry, representing the most emblematic consequence of a distorted foetal programming** and showing some **peculiar characteristics even at the molecular level..**

It is significant that the **MLL gene, which is very often involved** in these forms, **encodes a histone methyltransferase,** an enzyme with a key role in the implementation of **epigenetic and chromatin modifications, in the early stages of foetal development and differentiation of tissues** (especially in *haematopoiesis*), as pointed by Tomatis in his last article ..

www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2015;4(2):e040237
doi: 10.7363/040237
Received: 2015 Sept 21; accepted: 2015 Oct 10; published online: 2015 Oct 26

Editorial

Environment and fetal programming: the origins of some current "pandemics"

Ernesto Burgio

ECERI – European Cancer and Environment Institute, Bruxelles, Belgium
ISDE – International Society of Doctors for Environment (Scientific Office), Arezzo, Italy

"The womb may be more important than the home"
David Barker

This new paradigm is important not only to explain in a more exhaustive way the embryo-foetal origins of all the above mentioned disorders and their dramatic increase over the last decades, but also to try to effectively face this epidemiological transition. The key-term in this context is certainly primary prevention: only by reducing the maternal-foetal factors of distress and the exposure of the foetus (and of its gametes) to pollutants, it would be possible to protect the correct programming of cells, tissues and organs.

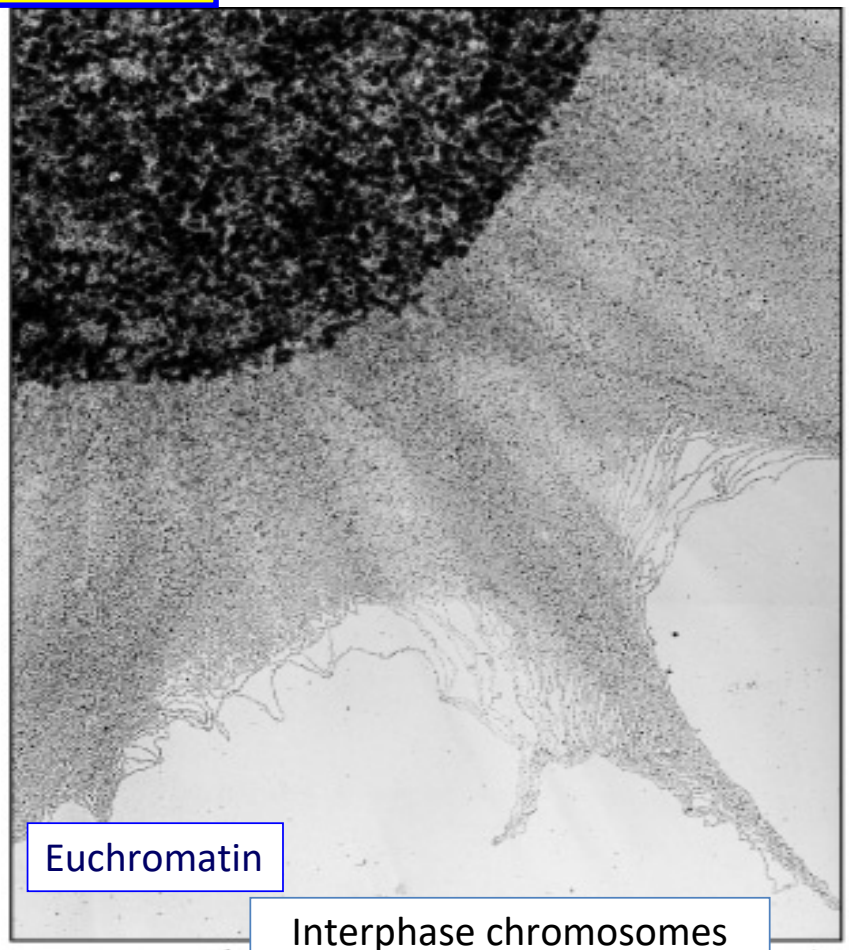
The key-term in this context is certainly ***primary prevention***

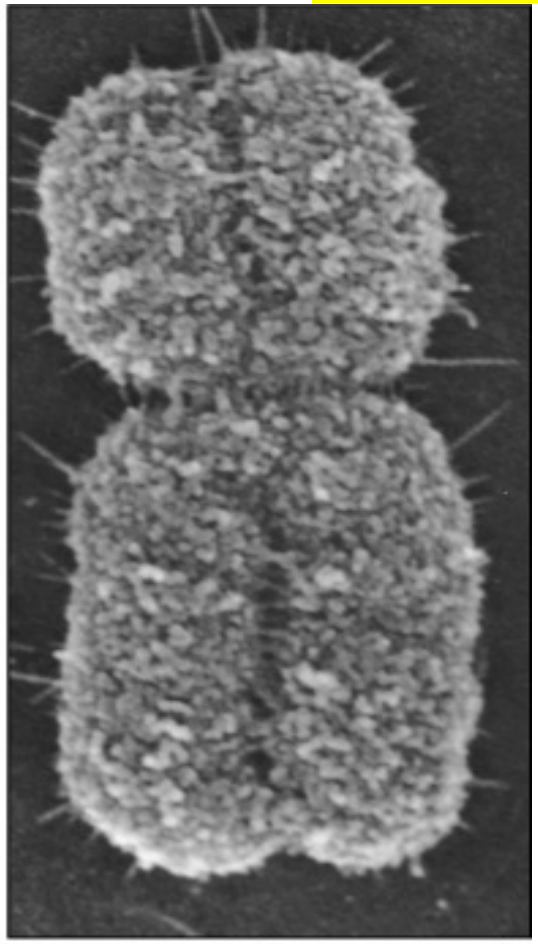
The first keyword: **Epigenetics**

Heterochromatin

Mitotic chromosome

At this point we can affirm that **epigenetics appears to be the part of molecular biology that allows us to better understand and, in perspective, to cure chronic pathologies and cancer** ..

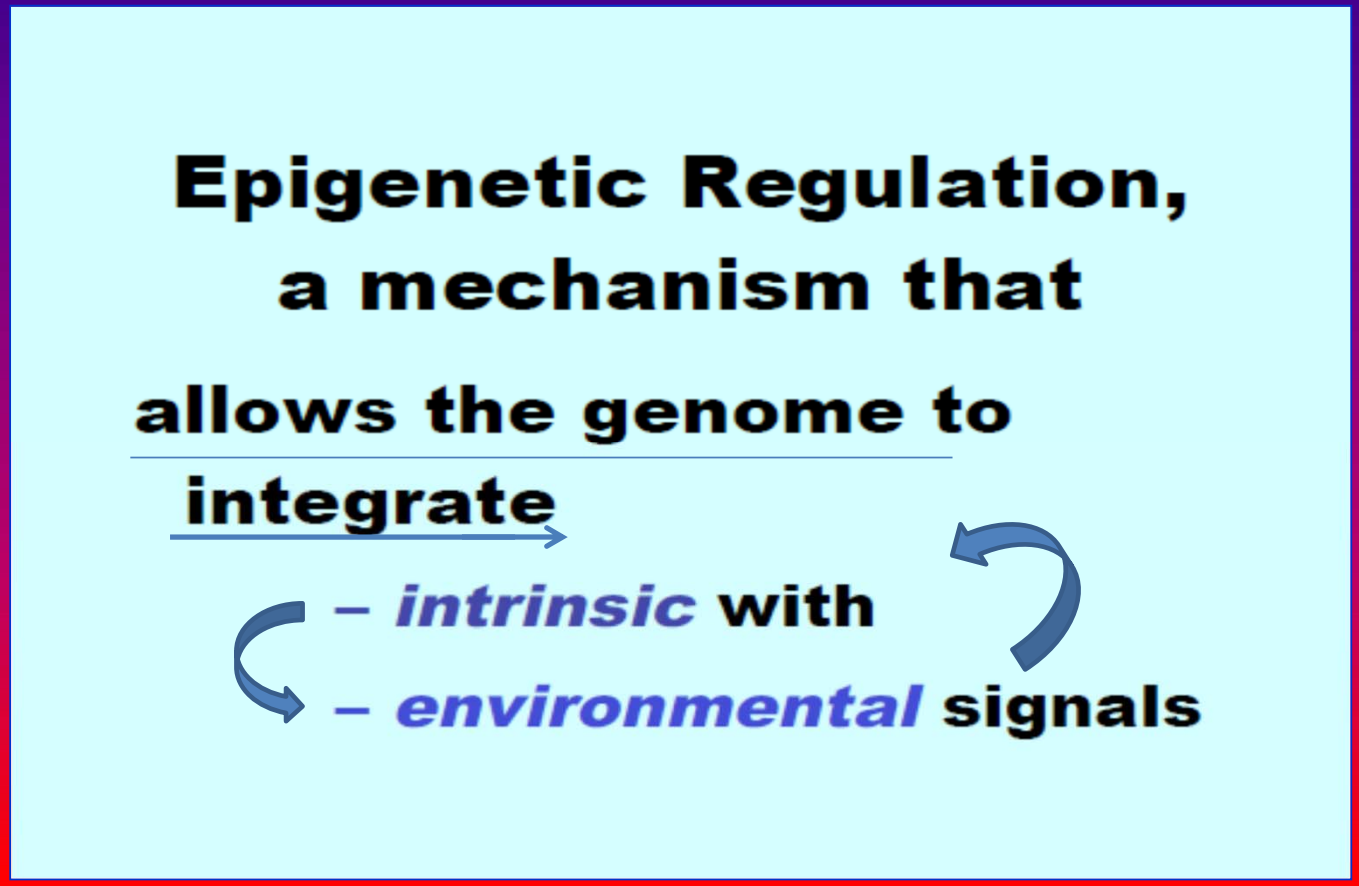




. if only we recognize **the *epigenome* as the active part of a new model of genome, systemic, fluid, open to environmental information and able to self-modify..**

Figure 4–21. Molecular Biology of the Cell, 4th Edition.

In such a fluid and systemic model the *epigenome* (also defined by some scientists as the controlling *software* of the genome) behaves as a sort of *Black Box/compensation chamber* - the specific place where the flow of information that comes from outside (*environment* and *microenvironment*) meets and interacts with the information encoded in the genes for millions years (the *hardware*)



Rudolf Jaenisch- Whitehead Institute and Dept. of Biology, MIT, Cambridge, MA

***Transposable elements can be seen as a natural genetic engineering system* acting** not just on one location at a time but **on the genome as a whole** ..This dynamic view of the genome has been illustrated most impressively by Jim Shapiro who stated that **the genome is composed of modular units arranged in a "*Lego-like*" manner and can modify itself under circumstances**

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Gene 345 (2005) 91–100

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Review

A 21st century view of evolution: genome system architecture, repetitive DNA, and natural genetic engineering

James A. Shapiro

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The last 50 years of molecular genetics have produced an abundance of new discoveries and data that make it useful to revisit some basic concepts and assumptions in our thinking about genomes and evolution. Chief among these observations are the complex modularity of genome organization, biological ubiquity of mobile and repetitive DNA sequences, and the fundamental importance of DNA rearrangements in the evolution of sequenced genomes. This review will take a broad overview of these developments and suggest some new ways of thinking about genomes as sophisticated informatic storage systems and about evolution as a systems engineering process.

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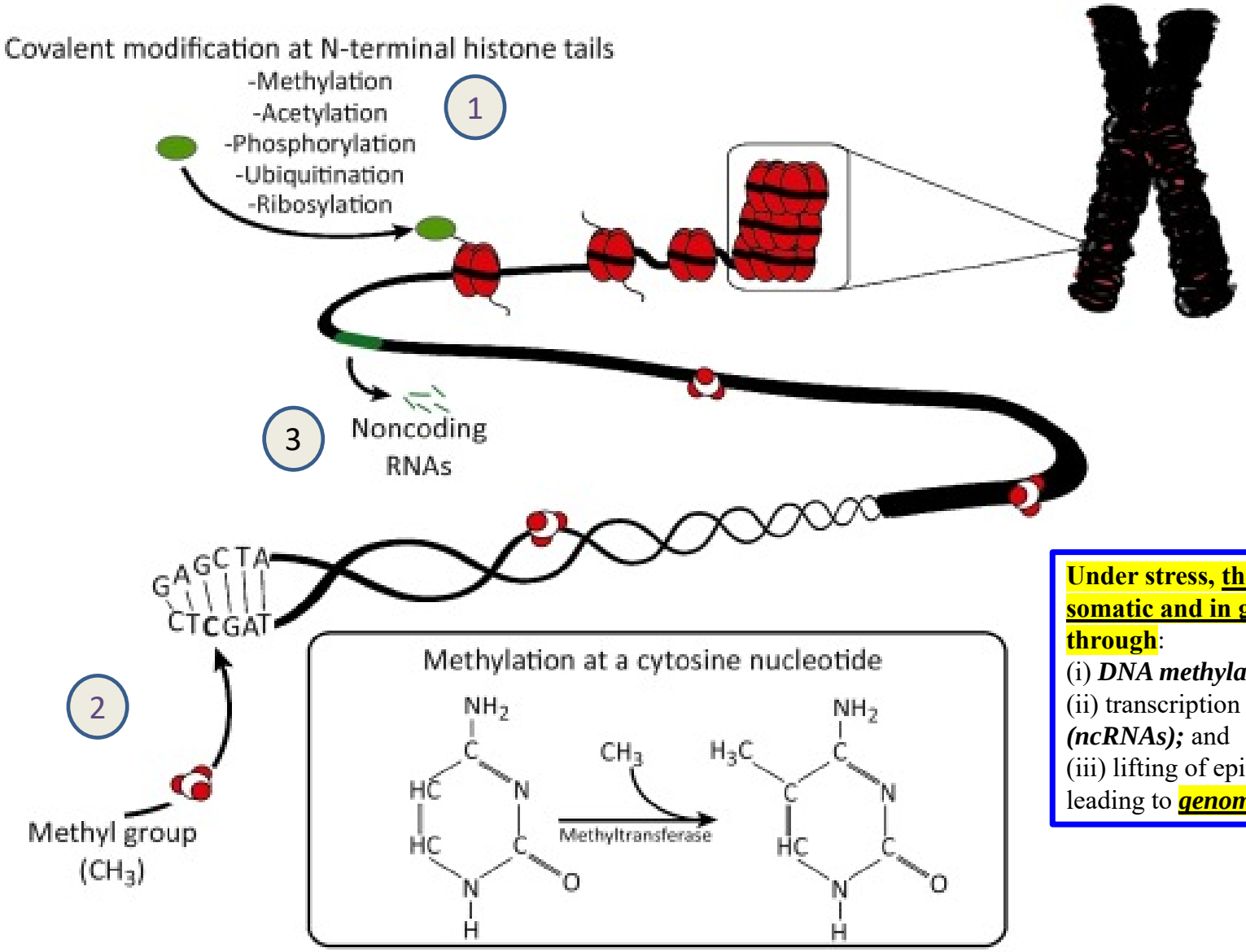
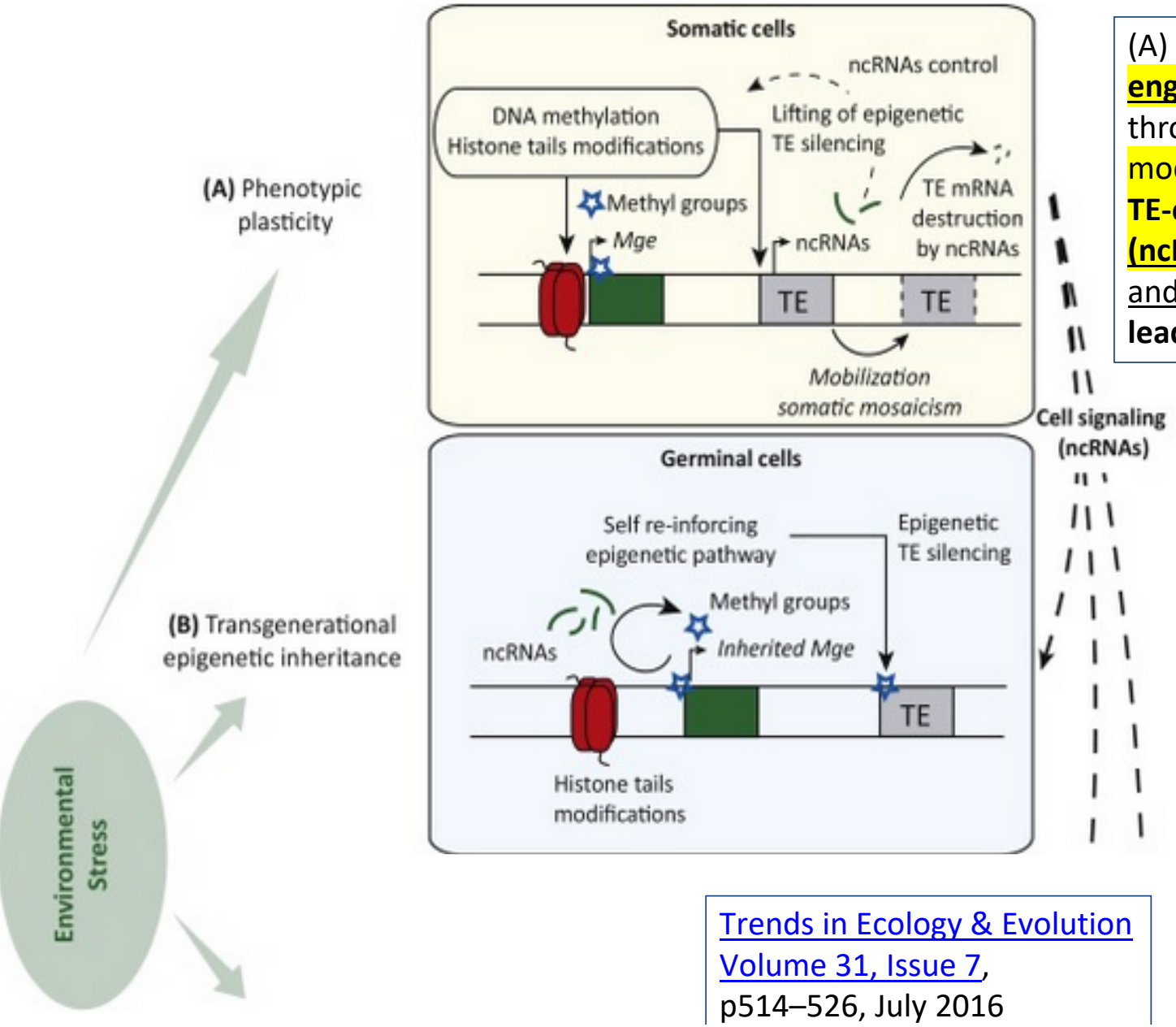


Trends in Ecology & Evolution

Adaptation to Global Change: A Transposable Element–Epigenetics Perspective

Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016

Under stress, the activation of the TE–EC engine both in somatic and in germ cells induces plastic responses through:
(i) ***DNA methylation*** and/or ***modifications of histone tails***;
(ii) transcription of TE-encoded ***regulatory noncoding RNAs (ncRNAs);*** and
(iii) lifting of epigenetic silencing and ***mobilization of TEs***..
leading to ***genome/plasticity*** and ***cells' mosaicism.***



(A) **Under stress, the activation of the TE–EC engine** in somatic cells induces **plastic responses** through: (i) DNA methylation and/or modifications of histone tails; (ii) **transcription of TE-encoded regulatory noncoding RNAs (ncRNAs)**; and (iii) lifting of epigenetic silencing and **mobilization of TEs in somatic cells**, **leading to somatic mosaicism.**

(B) **Stress induces epigenetic modifications in germline cells**. The resulting **phenotypes can be stabilized over generations (transgenerational epigenetic inheritance) through self-reinforcing epigenetic pathways**.

Stress perceived in somatic cells can also induce the **production of circulating ncRNAs that may modify the epigenome of remote germline cells** [dashed arrow from (A) to (B)].

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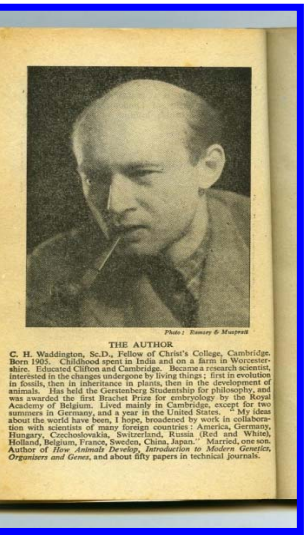
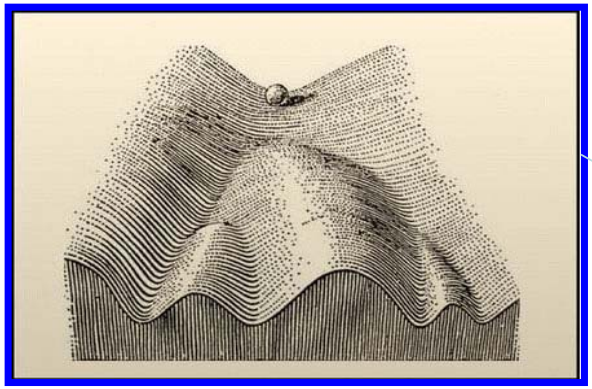
Relative frequency of articles with *epigenetics* in their title

Foreword 1



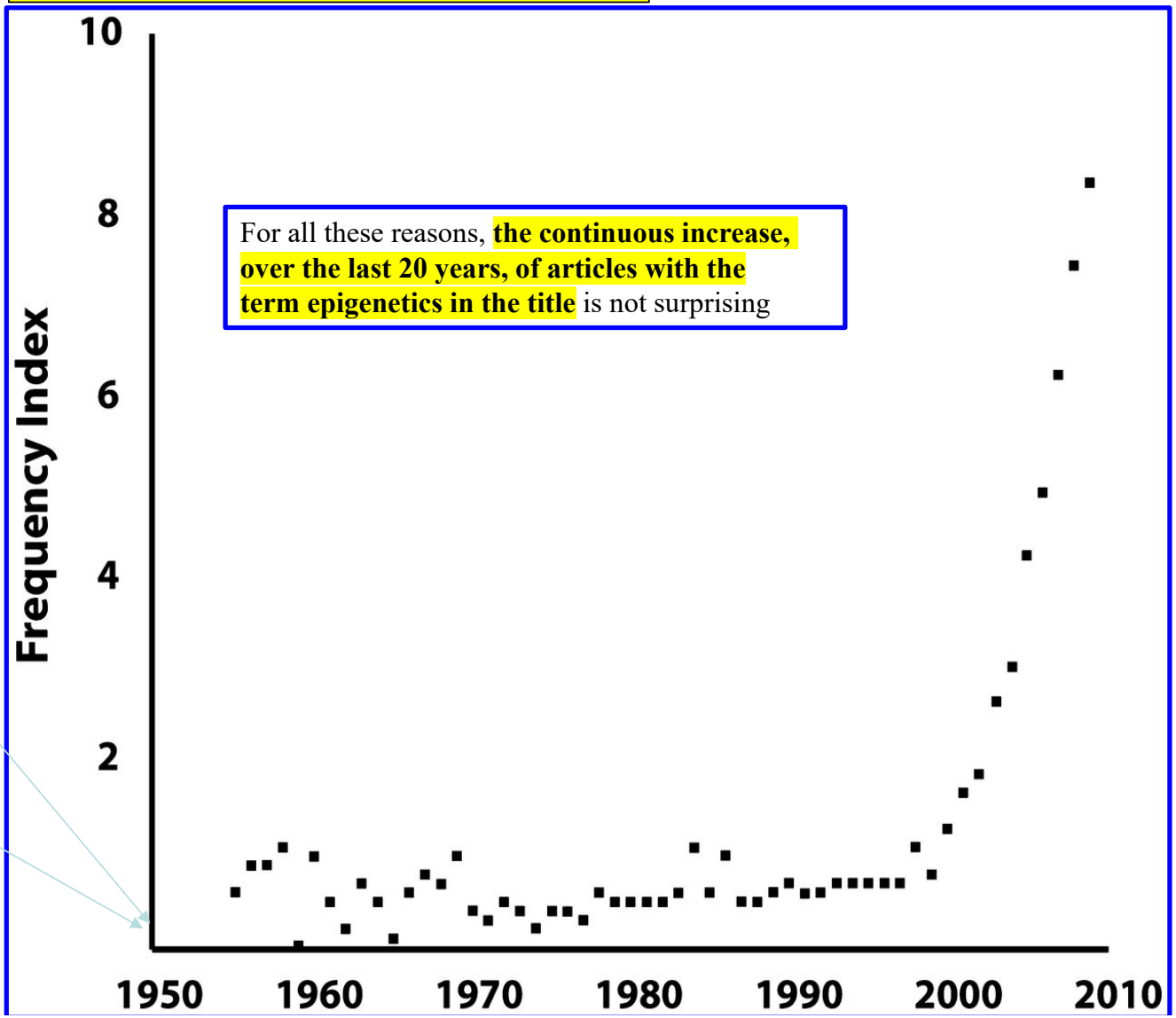
THE AUTHOR

C. H. Waddington, Sc.D., Fellow of Christ's College, Cambridge. Born 1905. Childhood spent in India and on a farm in Worcestershire. Educated Clifton and Cambridge. Became a research scientist, interested in the changes undergone by living things; first in evolution in fossils, then in inheritance in plants, then in the development of animals. Has held the Gerstenberg Studentship for philosophy, and was awarded the first Brachet Prize for embryology by the Royal Academy of Belgium. Lived mainly in Cambridge, except for two summers in Germany, and a year in the United States. My ideas about the world have been, I hope, broadened by work in collaboration with scientists of many foreign countries: America, Germany, Hungary, Czechoslovakia, Switzerland, Russia (Red and White), Holland, Belgium, France, Sweden, China, Japan." Married, one son. Author of *How Animals Develop*, *Introduction to Modern Genetics*, *Organizers and Genes*, and about fifty papers in technical journals.

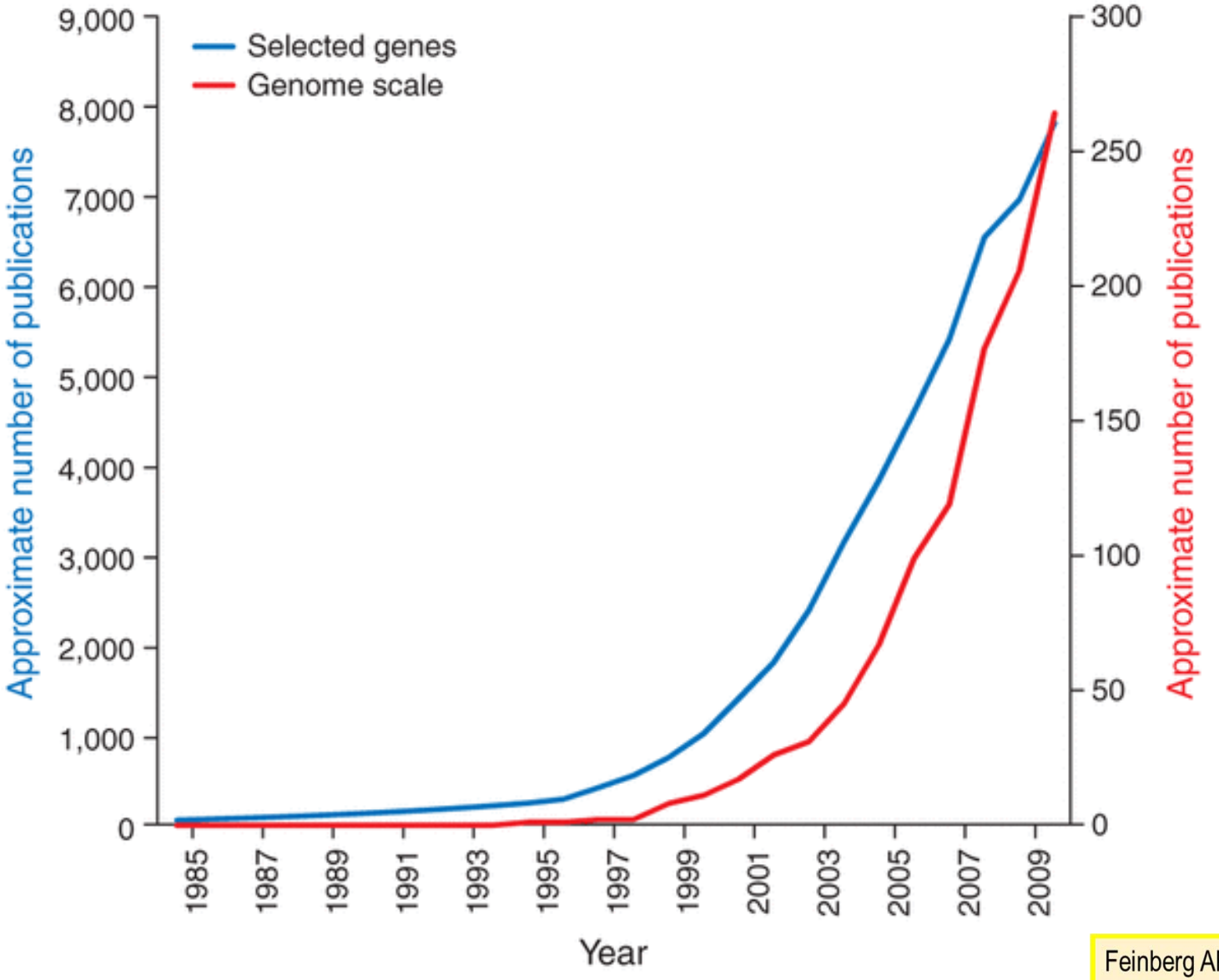


David Haig Int. J. Epidemiol. 2012;41:13-16

International Journal of Epidemiology



For all these reasons, **the continuous increase, over the last 20 years, of articles with the term epigenetics in the title** is not surprising

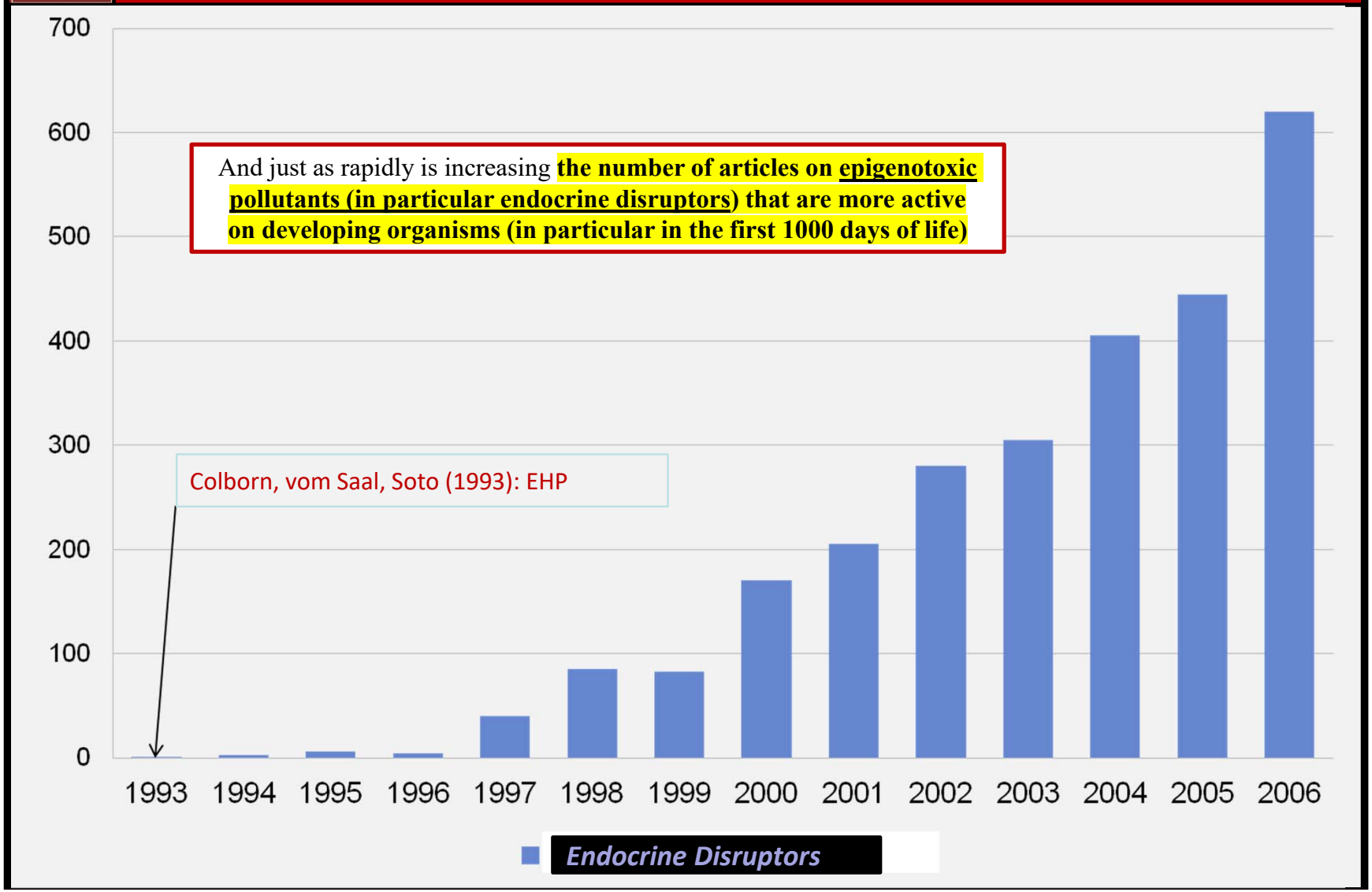


Also the **rate of increase** of **publications addressing *cancer (epi)genomics*** has become **greater than that of publications focused on selected genes**

Feinberg AP **Epigenomics reveals a functional genome anatomy and a new approach to common disease** Nature Biotechnology 28, 1049–1052 (2010)

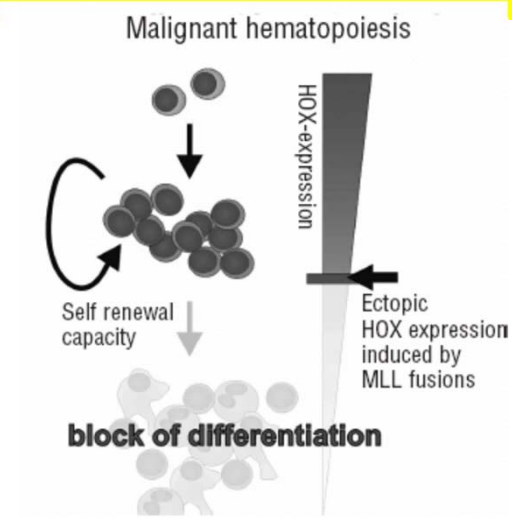
ACADEMY FOR ENVIRONMENTAL MEDICINE

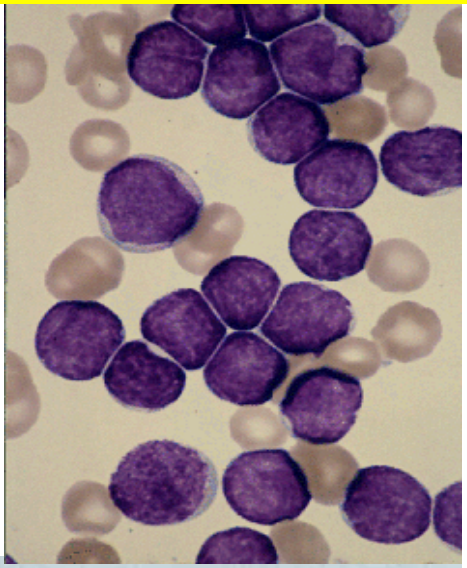
Published papers about *Endocrine Disruptors* between 1993 and November 2006 (Gies)

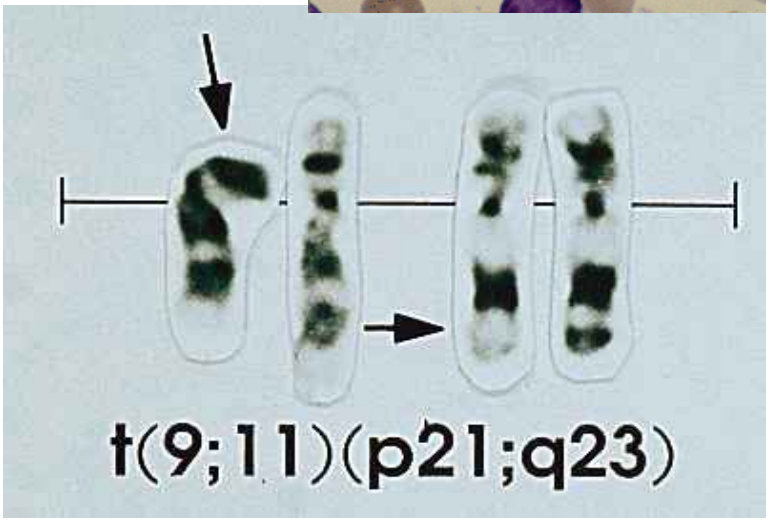


Translocations typical of myeloid leukaemia, probably due to maternal exposure to some toxic compound, were shown to be **present at birth in children who developed the disease years later** (while not sufficient per se to cause the disease, they might increase the risk for leukaemia by inducing genomic instability) Tomatis L. ***Identification of carcinogenic agents and primary prevention of cancer.*** Ann N Y Acad Sci. 2006 Sep;1076:1-14

Translocation **involving band 11q23 in AML** may occur as a result of a **deletion or trans-locations** with a number of other chromosomes and is usually associatedwith **M4** or **M5** and a poor prognosis







MLL (myeloid/lymphoid or mixed lineage leukemia)

Moreover this gene is involved in **dozens of different translocations** that express **fusion proteins, interfering with differentiation of pluripotent hematopoietic stem cells and dysregulating the expression patterns of HOX developmental genes…**

IN ALL AND AML, THE ***ALL1*** (ALSO NAMED ***MLL***) GENE CAN **FUSE WITH 1 OF MORE THAN 50 GENES**. **ALL1 IS PART OF A MULTIPROTEIN COMPLEX**. MOST OF THE PROTEINS IN THE COMPLEX ARE COMPONENTS OF **TRANSCRIPTION COMPLEXES**; OTHERS ARE INVOLVED IN **HISTONE METHYLATION AND RNA PROCESSING.** THE ENTIRE **COMPLEX REMODELS, ACETYLATES, DEACETYLATES, AND METHYLATES NUCLEOSOMES** AND **HISTONES**. THE **FUSION OF ALL1 WITH 1 OF these 50 PROTEINS** RESULTS IN THE **FORMATION OF THE CHIMERIC PROTEINS** THAT UNDERLIE ALL AND AML.

ALL1 (MLL) FUSION PROTEINS DEREGULATE HOMEOBOX GENES (WHICH ENCODE TRANSCRIPTIONS FACTORS)..and micro**RNAs GENES SUCH AS *MIR191*.**

The first and most striking property of MLL fusion proteins is their incredible diversity. MLL has been found in **73 different translocations** and **54 partner genes** have been cloned (*http://atlasgeneticsoncology.org/Genes/MLL.html).*

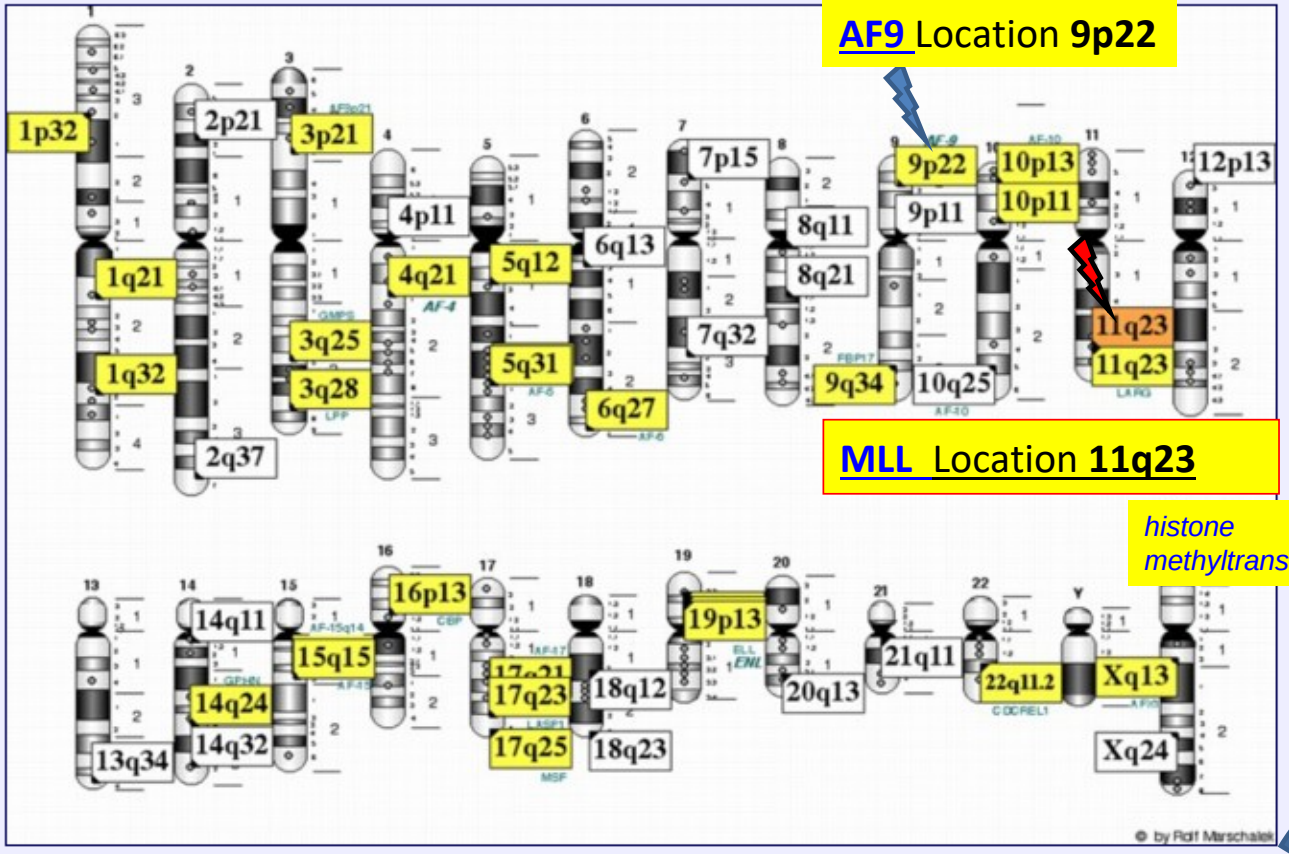
ALL1, HRX, Htrx (human trithorax), TRX1

MLL

11q23

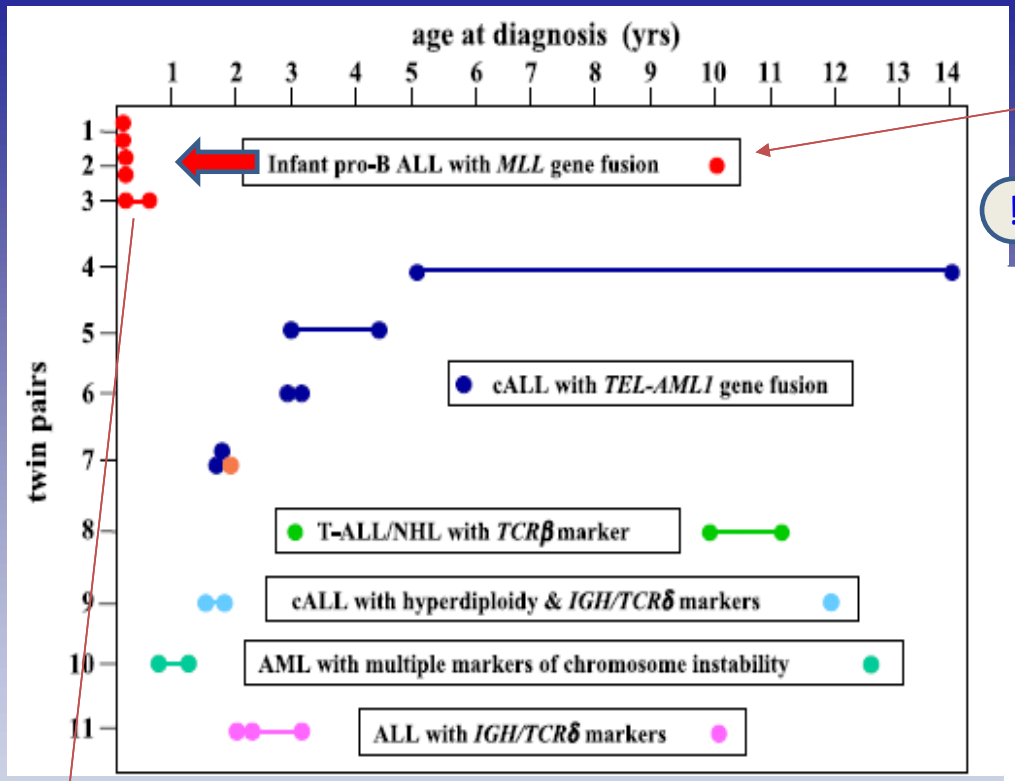
telomeric to PLZF, centromeric from RCK

Nakamura T, Mori T, Tada S, et al. ***ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation.*** Mol Cell 2002;10:1119-1128.



Several lines of evidence point to a mishap in non-homologous end joining of double strand breaks as the most likely reason for 11q23 translocations.

Figure 1 Concordant leukaemia in identical twins: the LRF Series (1993–2003). Figure illustrates age at diagnosis for each twin in the 11 pairs studied, the biological subtype of leukaemia and the molecular markers of clonality used.



MLL rearranged leukemias are associated with **poor prognosis** and **very brief latency** for MLL-AF4+ infant B ALL. This raises the question of how this disease can evolve so quickly,

!

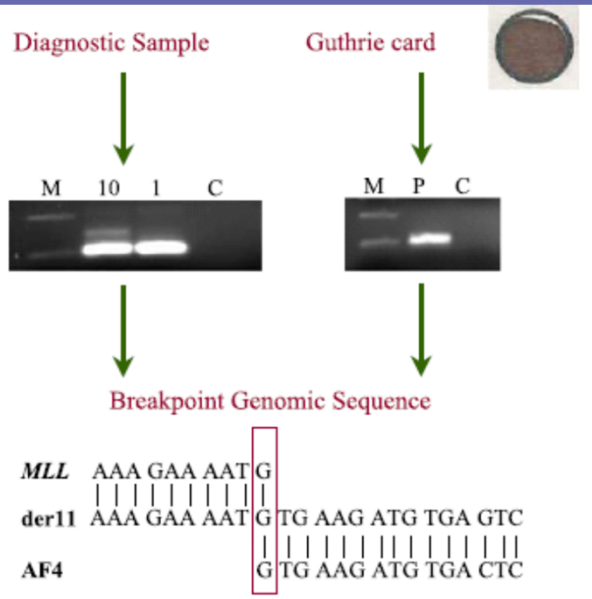


Figure 3 Detection of clonotypic fusion gene sequences (*MLL-AF4*) in neonatal blood spots (Guthrie card). 10, 1 μg DNA; C, control DNA; M, marker. Diagnostic DNA amplified by long-range PCR or long-distance inverse PCR [21]. Guthrie card DNA amplified by short-range (conventional) PCR using primers based on diagnostic DNA-derived genomic *MLL-AF4* sequence. Note diagnostic (leukaemic) DNA and Guthrie card contain the same unique *MLL-AF4* sequence as shown here for one case.

Even if **leukaemia fusion gene** formation is spontaneous, the risk of this occurring may be **modified by other factors, including folate availability**. There is dietary and genetic evidence that **folate has an impact on the risk of infant and childhood leukaemia ..**

!!

[CANCER RESEARCH 61, 2542–2546, March 15, 2001]

Transplacental Chemical Exposure and Risk of Infant Leukemia with *MLL* Gene Fusion[1]

Freda E. Alexander,[2] Sherry L. Patheal, Andrea Biondi, Silvia Brandalise, Maria-Elena Cabrera, Li C. Chan, Zhu Chen, Giuseppe Cimino, Jose-Carlos Cordoba, Long-Jun Gu, Hany Hussein, Eiichi Ishii, Azza M. Kamel, Silvia Labra, Isis Q. Magalhães, Shuki Mizutani, Eleni Petridou, Maria Pombo de Oliveira, Patrick Yuen, Joseph L. Wiemels, and Mel F. Greaves

Infant acute leukemia (IAL) frequently involves breakage and recombination of the *MLL* gene with one of several potential partner genes. These gene fusions arise *in utero* and are similar to those found in leukemias secondary to chemotherapy with inhibitors of topoisomerase II (topo-II). This has led to the hypothesis that *in utero* exposures to chemicals may cause IAL via an effect on topo-II. We report a pilot case-control study of IAL across different countries and ethnic groups. Cases ($n = 136$) were population-based in most centers. Controls ($n = 266$) were selected from inpatients and outpatients at hospitals serving the same populations.

ing Baygon). Elevated odds ratios were observed for MLL^{+ve} (but not MLL^{-ve}) leukemias (2.31 for DNA-damaging drugs, $P = 0.03$; 5.84 for dipyrone, $P = 0.001$; and 9.68 for mosquitocidals, $P = 0.003$). Although it is unclear at present whether these particular exposures operate via an effect on topo-II, the data suggest that specific chemical exposures of the fetus during pregnancy may cause *MLL* gene fusions. Given the widespread use of dipyrone, Baygon, and other carbamate-based insecticides in certain settings, confirmation of these apparent associations is urgently required.

Also the **high frequency of MLL1-gene rearrangements in leukaemias and myelodysplastic syndromes secondary to treatment with topoisomerase II inhibitors** is a significant argument in favour of **prenatal and (epi)genotoxic origin of infant leukaemia, due to maternal and foetal exposure to substances** - such as ***bioflavonoids*** (contained in many foods), and widely used insecticides, such as ***dipyrone (Baygon)*** - **interfering with the action of this enzyme (which is essential for the unwinding of the double helix**).

Propoxur (***Baygon***°) is also widely used against cockroaches, fleas, and similar pests. Therefore, it is important that the associations observed in this study are reevaluated in an extended case-control study

Finally, it has been known for at least 20 years **that the mother's residence during pregnancy is a more reliable index of in utero exposure** and correlates with the **incidence of childhood leukemia**

EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Childhood cancers and atmospheric carcinogens

E G Knox

J Epidemiol Community Health 2005;**59**:101–105. doi: 10.1136/jech.2004.021675

Main results: Significant birth proximity relative risks were found within 1.0 km of hotspots for carbon monoxide, PM10 particles, VOCs, nitrogen oxides, benzene, dioxins, 1,3-butadiene, and benz(a)pyrene. Calculated attributable risks showed that most child cancers and leukaemias are probably initiated by such exposures.

Conclusions: Reported associations of cancer birth places with sites of industrial combustion, VOCs uses, and associated engine exhausts, are confirmed. Newly identified specific hazards include the known carcinogens 1,3-butadiene, dioxins, and benz(a)pyrene. The mother probably inhales these or related materials and passes them to the fetus across the placenta.

Key points

Childhood cancer/leukaemia births are closely associated with high atmospheric emissions from combustion processes, mainly oil based, and from organic evaporation. Demonstrated associations with 1–3,butadiene, dioxins, and benz(a)pyrene, but possibly others as well, are probably causal. Such toxic emissions may account for a majority of all cases.

Some years ago we have already shown **that the embryo-fetal (and epigenetic!) origins of childhood cancer had already been discovered 150 years ago** by some students of the great German pathologist **Virchow..** who had already recognized at the light microscope the ***precancerous stem cells*** as "***dormant embryonic remnants that could be activated to become cancer by a "disequilibrium" in the surrounding tissue***..

Mol Biol Rep
DOI 10.1007/s11033-014-3804-3

Published online: 12 November 2014

Springer

Towards a systemic paradigm in carcinogenesis: linking epigenetics and genetics

Ernesto Burgio · Lucia Migliore

Abstract For at least 30 years cancer has been defined as a genetic disease and explained by the so-called somatic mutation theory (SMT), which has dominated the carcinogenesis field. Criticism of the SMT has recently greatly increased, although still not enough to force all SMT supporters to recognize its limits. Various researchers point out that cancer appears to be a complex process concerning a whole tissue; and that genomic mutations, alth… variably deleterious and unpredictably important in deter- mining the establishment of the ne… not the primary origin for a ma… attempt to describe the inadequa… demonstrate that epigenetics is a … carcinogenesis.

Is the **carcinogenic process the ontogenic development gone awry ?**

… and the main cause of cancer **a block in cell differentiation programs (just the "hallmark", inexplicably neglected by major theorists of SMT)** ?

The *Embryonic Rest Theory* and the field theories of cancer

Some **Virckow**'s followers (1870 ca) formulated the theory that **adult tissues contain *dormant embryonic remnants* that could be activated to become cancer**
Perhaps the most intriguing aspect of the theory concerned the **hypothesized trigger of the process: ..a change in the environment, a "disequilibrium" in the surrounding tissue,** that **would induce these embryonic remnants to resume cell proliferation and to produce masses of cells resembling fetal tissues (*field theory*)**

Mol Biol Rep
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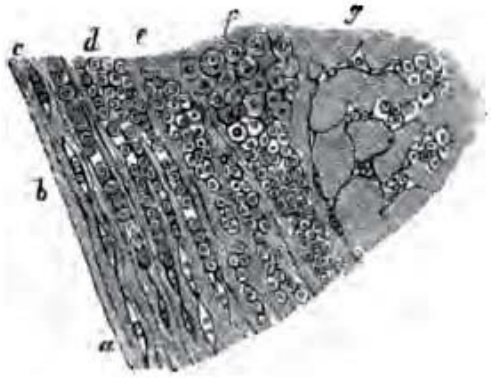
The Embryonic Rest Theory and the field theories of cancer

Towards a systemic paradigm in carcinogenesis: linking epigenetics and genetics

Ernesto Burgio · Lucia Migliore

From **Cellular Pathology**: *Development of cancer from connective tissue in the carcinoma of the breast*



Virchow, Rudolf. ***Cellular Pathology as Based Upon Physiological and Pathological Histology***. London, 1860

Virchow and other well known pathologists, on observing cancer tissue under the microscope, noted the **similarity between embryonic tissue and cancer,** and suggested that **tumors arise from embryo-like cells** [105].

On this basis, some Virckow's followers [106-107] formulated the **theory that adult tissues contain *dormant embryonic remnants* that could be activated to become cancer**.

Perhaps the most intriguing aspect of the theory concerned the **hypothesized trigger** of the process: it would be **a change in the environment, a "disequilibrium" in the surrounding tissue,** that **would induce these embryonic remnants to resume cell proliferation and to produce masses of cells that resembled fetal tissues (*field theory*).**

Abstract For at least 30 years cancer has been defined as a genetic disease and explained by the so-called somatic mutation theory (SMT), which has dominated the carcinogenesis field. Criticism of the SMT has recently greatly increased, although still not enough to force all SMT supporters to recognize its limits. Various researchers point out that cancer appears to be a complex process concerning a whole tissue; and that genomic mutations, although variably deleterious and unpredictably important in determining the establishment of the neoplastic phenotype, are not the primary origin for a malignant neoplasia. We attempt to describe the inadequacies of the SMT and demonstrate that epigenetics is a more logical cause of carcinogenesis. Many previous models of carcinogenesis fall into two classes: (i) in which some biological changes inside cells alone lead to malignancy; and (ii) requiring changes in stroma/extracellular matrix. We try to make clear that in the (ii) model genomic instability is induced by persistent signals coming from the microenvironment, provoking epigenetic and genetic modifications in tissue stem cells that can lead to cancer. In this perspective, stochastic mutations of DNA are a critical by-product

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Cancer as a genetic disease: the somatic mutation theory

The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease [1]

The genetic basis of cancer was first recognised in 1902 by the German zoologist Theodor Boveri, who postulated that chromosomes transmitted inheritance factors, proposed the existence of cell cycle check points [2]; suggested that mutations of the chromosomes could generate a cell with unlimited growth potential which could be passed onto its descendants; observed aneuploidy in cancer cells that had acquired the potential for uncontrolled continuous proliferation [3]; speculated that cancers might be caused or promoted by radiation, physical or chemical insults or

The great lesson of *teratocarcinoma* and the stem cell theory of cancer

- the **transplantation of pluripotent or embryonic stem cells into adult mammals**, frequently leads to the growth of **teratocarcinomas**
- the **microenvironment** was central to this paradigm-breaking findings: the origin of the teratoma was a "dissonance"..
- intriguingly, **putting the teratocarcinoma cells into an early mammal embryo at the blastocyst stage**.. they can **generate normal tissues in viable mosaic individuals ..**
- **normal offspring** could result from a… cancer cell
- normal germinal **stem cells who became cancerous, showed the potential to revert to normal cells if placed in embryo**

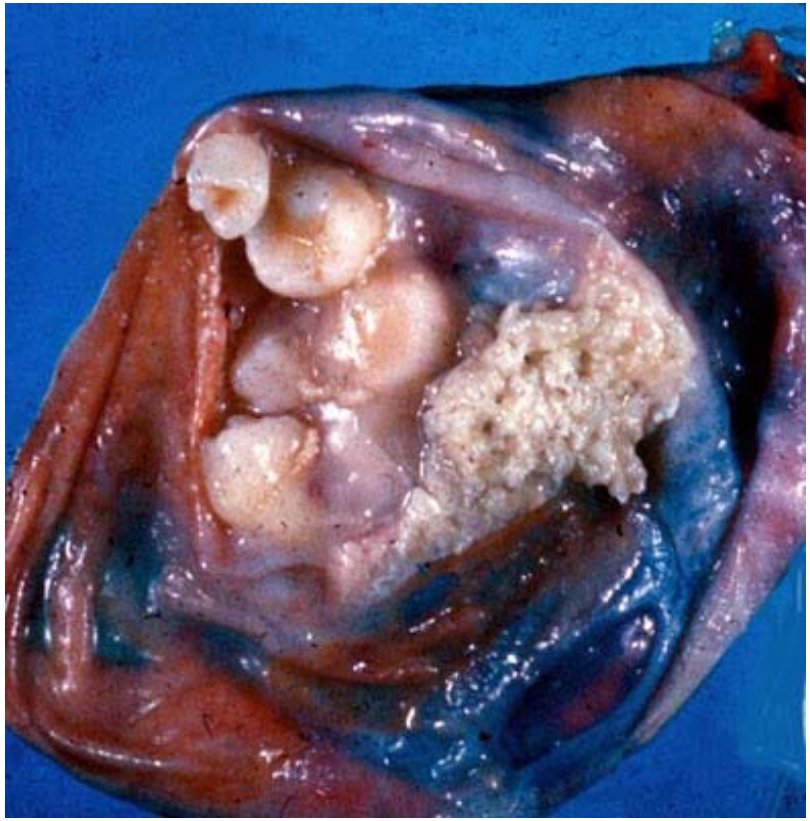
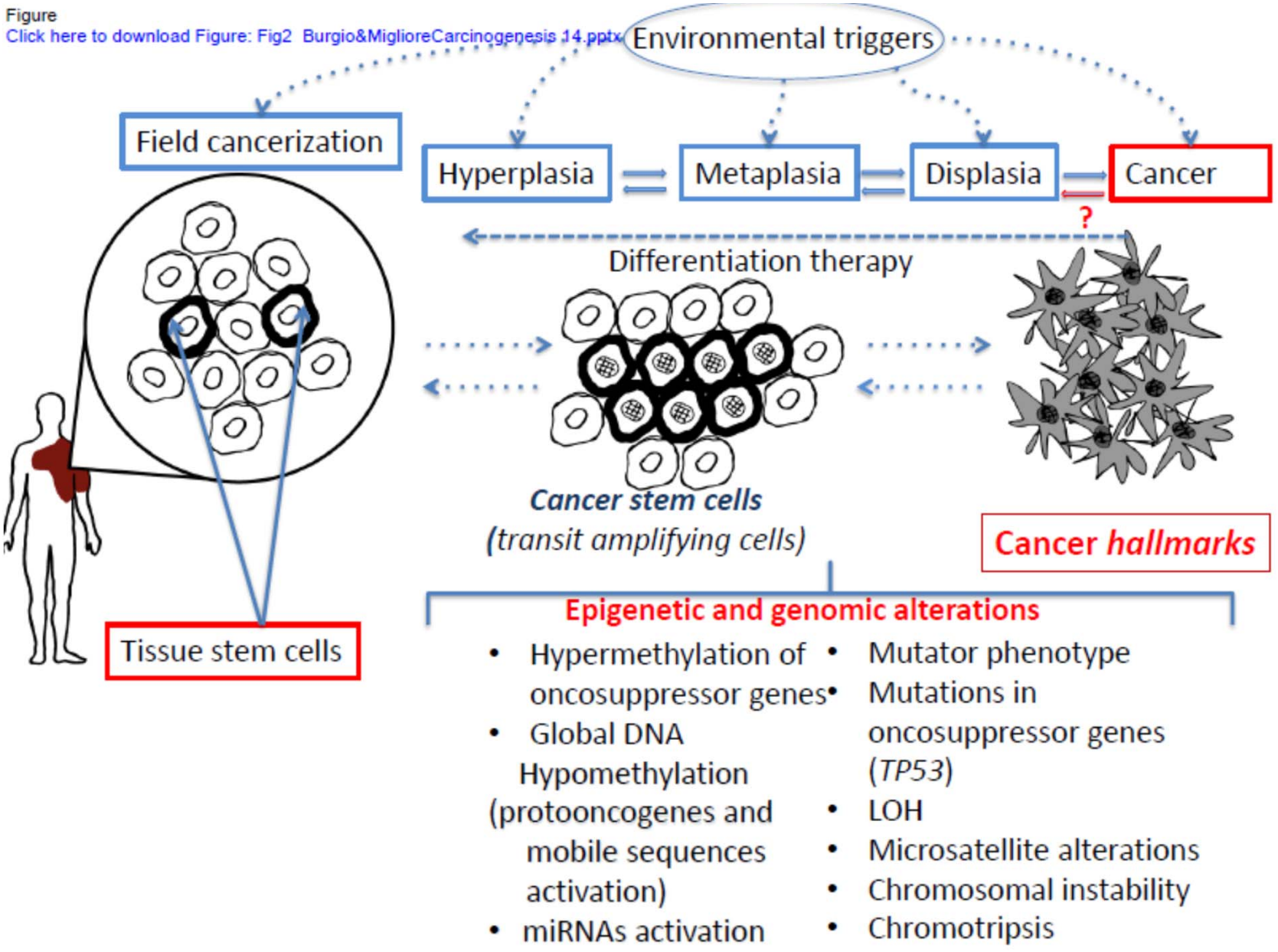


Figure
Click here to download Figure: Fig2 Burgio&MiglioreCarcinogenesis 14.pptx



Tissue repair and stem cell renewal in carcinogenesis

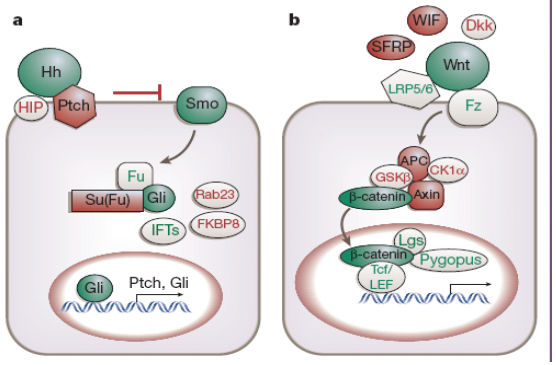
Nature. 2004 Nov 18;432(7015):324-31.

Philip A. Beachy[1,4], Sunil S. Karhadkar[1,2] & David M. Berman[2,3,4]

[1]Department of Molecular Biology and Genetics, The Howard Hughes Medical Institute, [2]Department of Pathology, [3]Department of Urology and [4]Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA (e-mail: pbeachy@jhmi.edu)

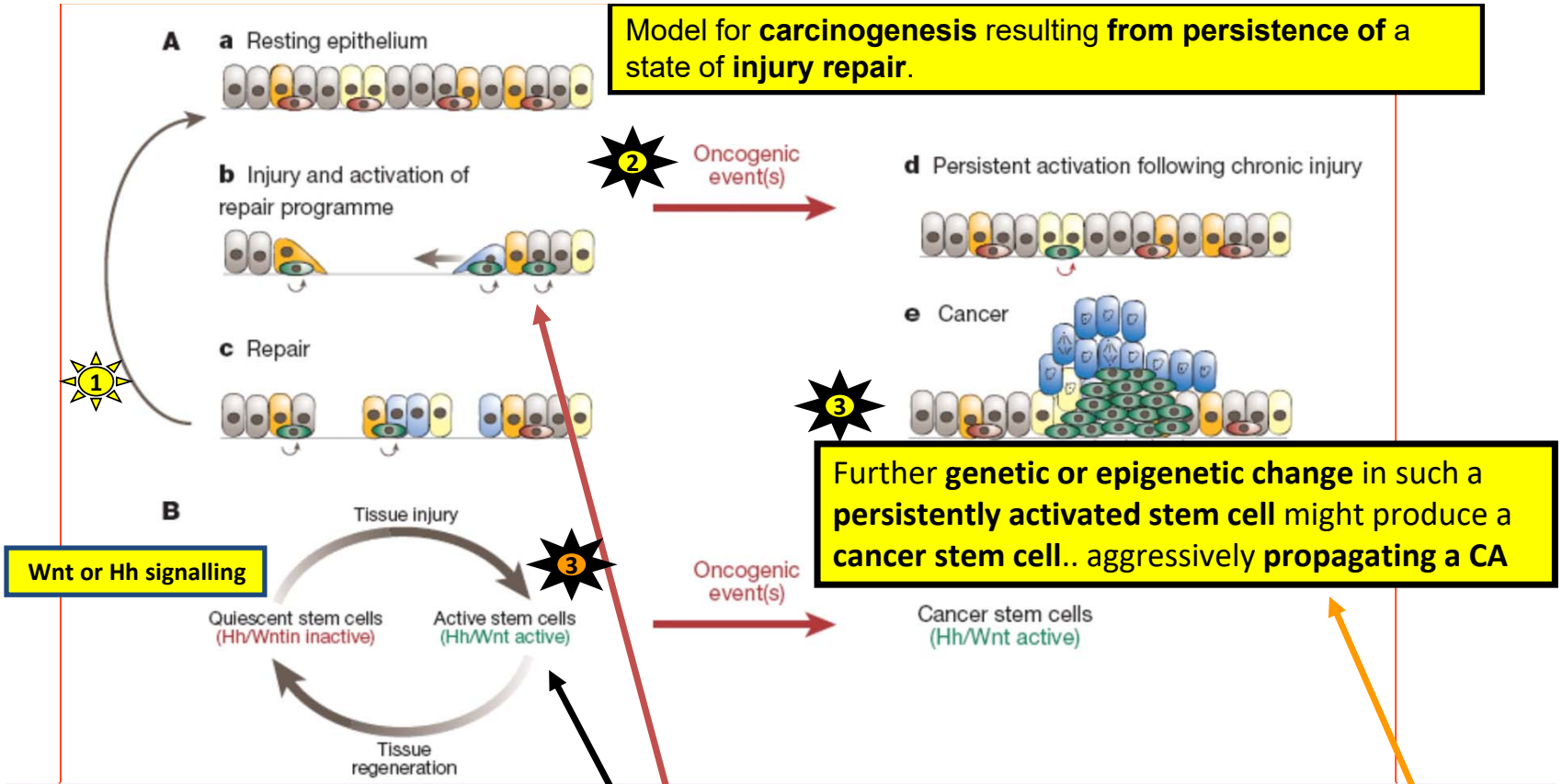
Cancer is increasingly being viewed as a stem cell disease, both in its propagation by a minority of cells with stem-cell-like properties and in its possible derivation from normal tissue stem cells. But stem cell activity is tightly controlled, raising the question of how normal regulation might be subverted in carcinogenesis. The long-known association between cancer and chronic tissue injury, and the more recently appreciated roles of Hedgehog and Wnt signalling pathways in tissue regeneration, stem cell renewal and cancer growth together suggest that carcinogenesis proceeds by misappropriating homeostatic mechanisms that govern tissue repair and stem cell self-renewal.

Figure 1 Hh and Wnt signalling pathways. Simplified views of the Hh and Wnt signalling pathways, with emphasis on components implicated in cancer or tissue regeneration. Green and red colours denote pathway components with primarily positive or negative roles, respectively, in pathway activation. Shaded components



Cancer is increasingly being viewed as a **stem cell disease**.. The **long-known association between cancer and chronic tissue injury,** and the more recently appreciated roles of **Hedgehog and Wnt signalling pathways in tissue regeneration, stem cell renewal and cancer growth** suggest that **carcinogenesis proceeds by misappropriating homeostatic mechanisms that govern tissue repair and stem cell self-renewal.**

Model for **carcinogenesis** resulting **from persistence of** a state of **injury repair**.



Further **genetic or epigenetic change** in such a **persistently activated stem cell** might produce a **cancer stem cell**.. aggressively **propagating a CA**

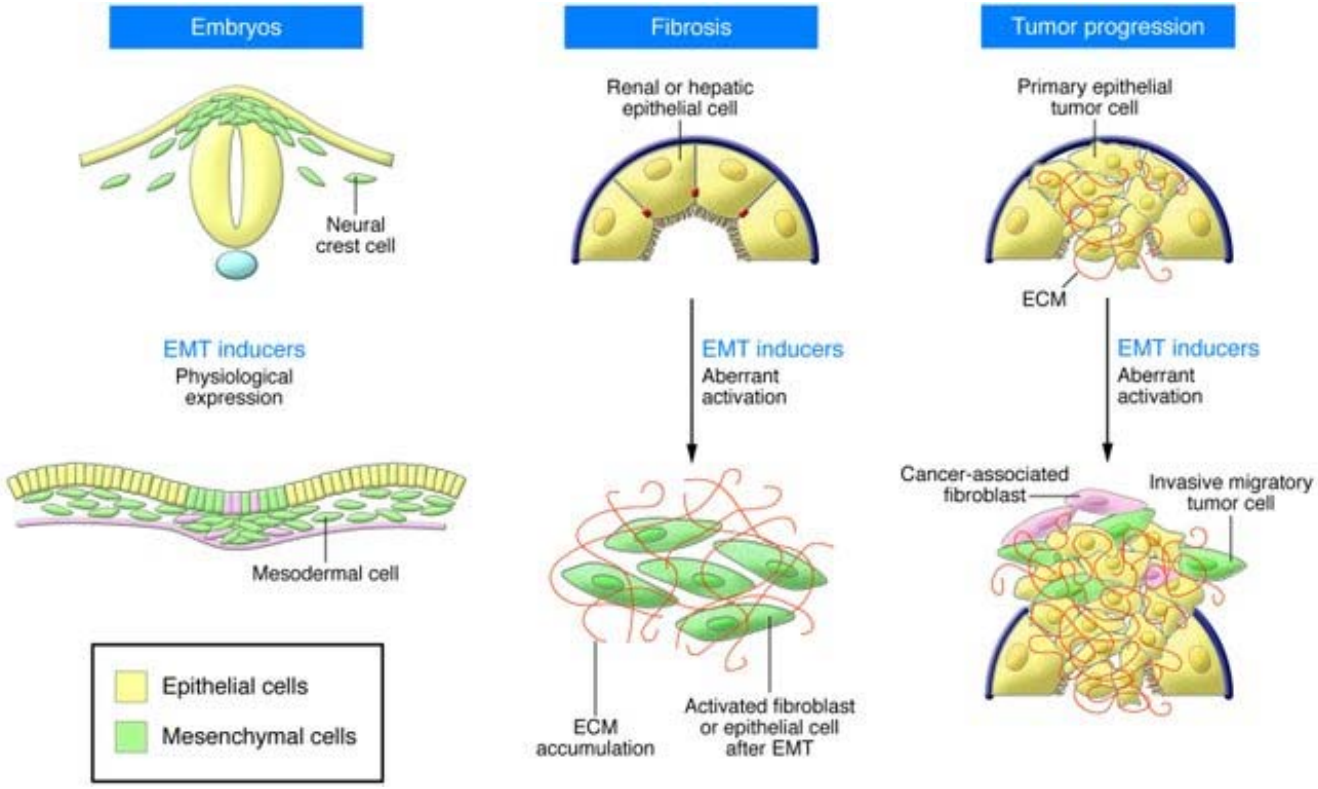
Figure 2 Model for carcinogenesis resulting from persistence of a state of injury repair. **A**, Cellular events of epithelial repair. **a**, Resting epithelium with several differentiated cell phenotypes (brown, orange, and yellow) derived from tissue stem cells, now quiescent (red). Pathways such as Hh and Wnt signalling pathways that have a role in the renewal of stem cells are not active. **b**, Epithelial defect resulting from acute injury. Loss of epithelial continuity activates a repair program which is driven by Hh or Wnt signalling. This program results in the acquisition by epithelial cells of a more mesenchymal phenotype, including flattening and movement of cells (straight arrow) to cover the wound, activation (green), and expansion of stem cells through renewal divisions (curved arrows). **c**, The wound is repaired, first by rapid cell movement, and then by restoration of cell numbers resulting from the amplification of stem cells and the differentiation of their progeny. Subsequently, either epithelial continuity and patterning is restored, Hh and Wnt signalling ceases, and the stem cell compartment returns to quiescence (**a**); or oncogenic event(s) may trap a stem cell in an activated state of continuous renewal, which is driven by autonomous Wnt or Hh signalling (**d**). Further genetic or epigenetic change in such a persistently activated stem cell (curved red arrows) might produce a cancer stem cell (green) which is capable of aggressively propagating a cancer (**e**). This may result from enhanced proliferation and production of more cancer stem cells as well as from differentiated cancer cells (blue). **B**, Stem cells cycle between quiescence and activity as a consequence of Hh/Wnt driven responses to injury. Oncogenic event(s) may trap activated stem cells in a permanent state of Hh/Wnt driven activity, resulting in cancer stem cells.

But, perhaps **the most significant datum in this model**, alternative to the dominant one (SMT), concerns **THE ONLY real cancer hallmark (which makes it a killer), i.e. the ability to give metastasis** ..
which **is NOT DUE TO ANY STOCHASTIC DNA MUTATION, but to the reactivation of an EPIGENETIC program (EMT), physiological in the embryonic period, which allows fetal cells to migrate towards their final location ..**

Review series

Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease

Hervé Acloque,[1] Meghan S. Adams,[2] Katherine Fishwick,[2] Marianne Bronner-Fraser,[2] and M. Angela Nieto[1]



J Clin Invest. 2009;119(6):1438–1449.

.. followed by a complementary EMBRYO-FETAL EPIGENETIC program (MET) that allows the same cells to stabilize in the reached site!

J Clin Invest. 2009;119(6):1417–1419.

EMT: When epithelial cells decide to become mesenchymal-like cells

Raghu Kalluri[1,2]

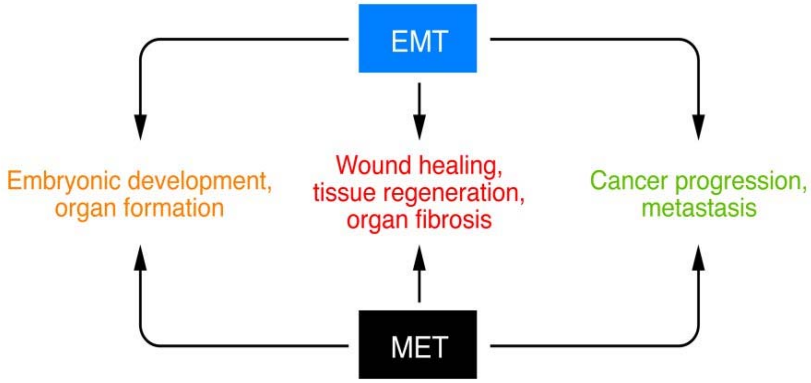
[1]Division of Matrix Biology, Beth Israel Deaconess Medical Center, and Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts, USA. [2]Harvard-MIT Division of Health Sciences and Technology, Boston, Massachusetts, USA.

Epithelial-mesenchymal transition (EMT) is critical for appropriate embryonic development, and this process is re-engaged in adults during wound healing, tissue regeneration, organ fibrosis, and cancer progression. Inflammation is a crucial conspirator in the emergence of EMT in adults but is absent during embryonic development. As highlighted in this Review series, EMT is now a recognized mechanism for dispersing cells in embryos, forming fibroblasts/mesenchymal cells in injured tissues, and initiating metastasis of epithelial cancer cells. Also discussed

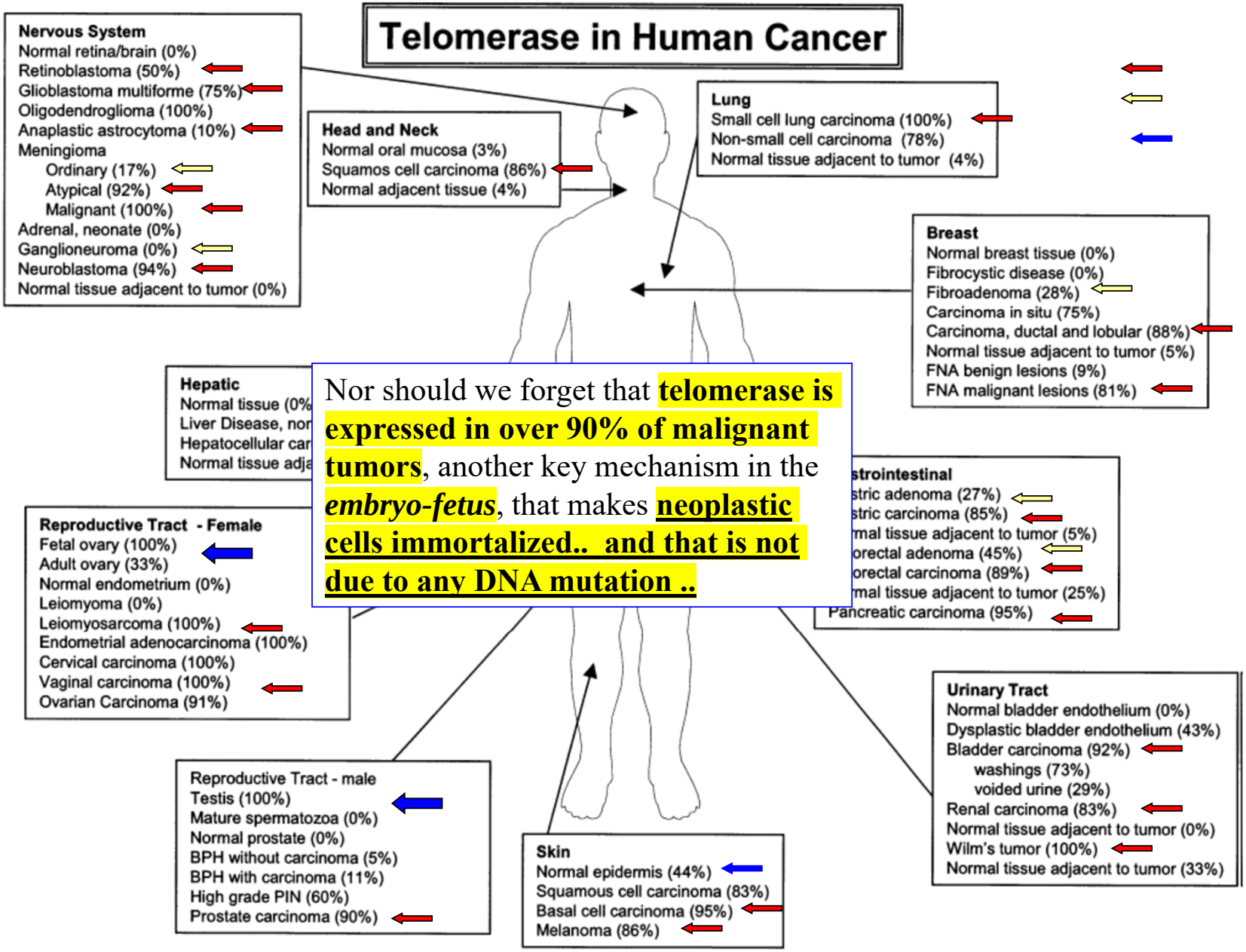
Cancer is a wound which never heals

Rudolf Virchow

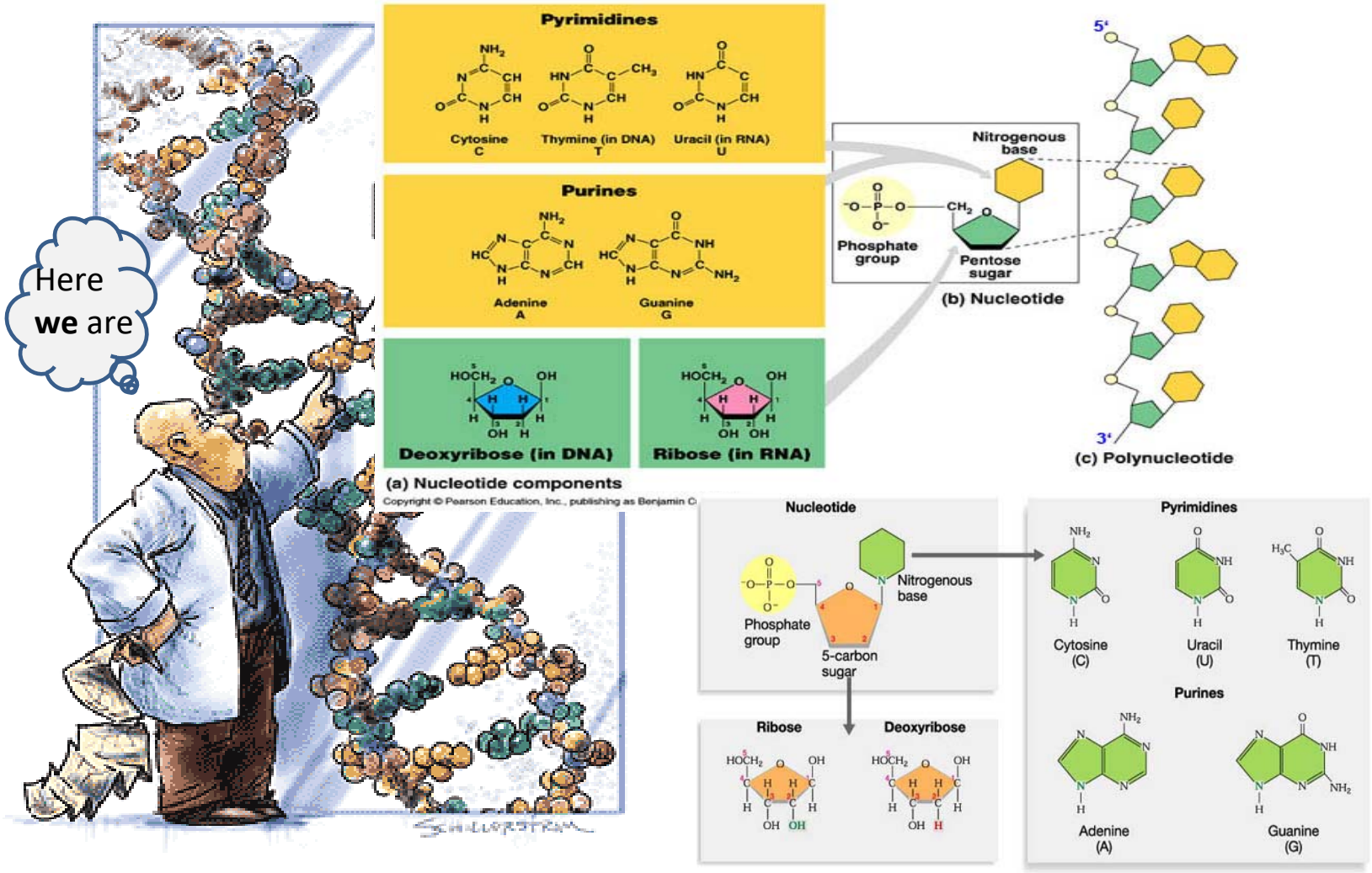
During **embryogenesis**, **epithelia** are considered to be **highly plastic** and able to **switch back and forth between epithelia and mesenchyme**, via the processes of **EMT** and mesenchymal-epithelial transition (**MET**), respectively... **terminally differentiated epithelia can change their phenotype (EMT ←→ MET) under the influence of repair-associated or pathological stress**



Epithelial-mesenchymal transition (**EMT**) is critical for **appropriate embryonic development… re-engaged** in adults during **wound healing, tissue regeneration, organ fibrosis**, and **cancer progression**.

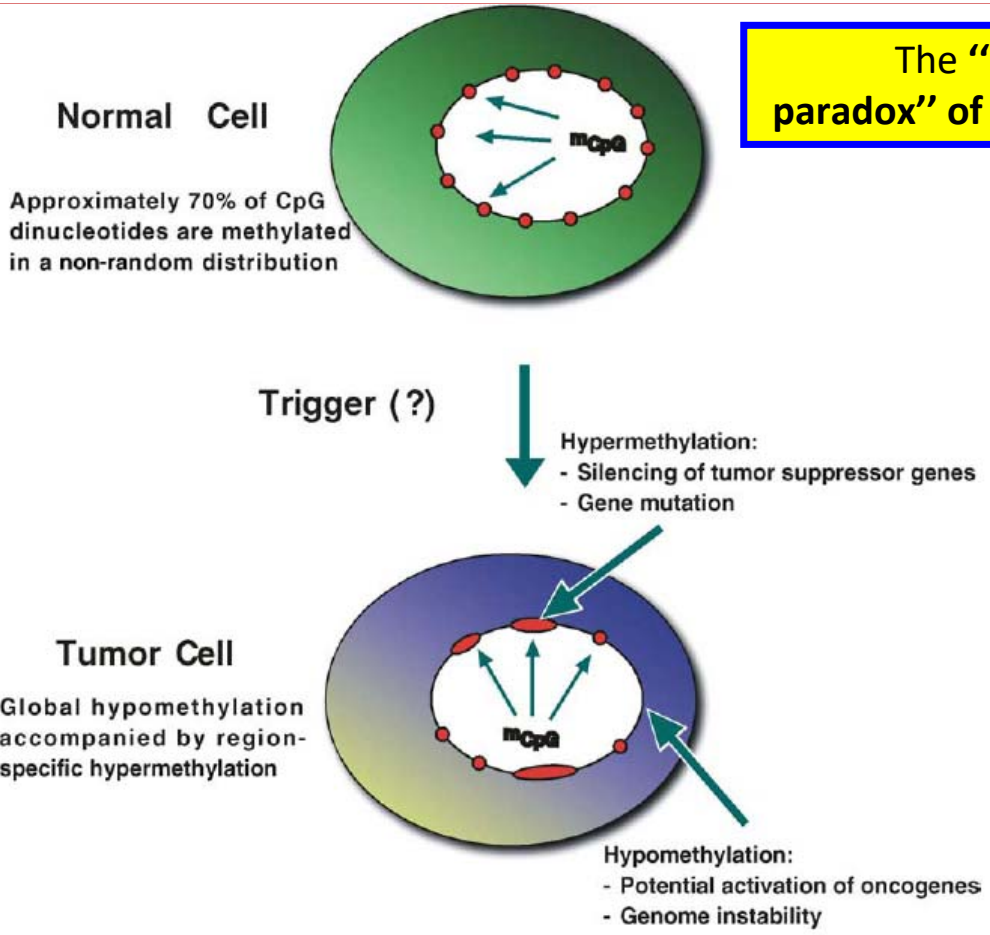

Telomerase in Human Cancer
Nervous System
Normal retina/brain (0%)
Retinoblastoma (50%)
Glioblastoma multiforme (75%)
Oligodendroglioma (100%)
Anaplastic astrocytoma (10%)
Meningioma
Ordinary (17%)
Atypical (92%)
Malignant (100%)
Adrenal, neonate (0%)
Ganglioneuroma (0%)
Neuroblastoma (94%)
Normal tissue adjacent to tumor (0%)
Head and Neck
Normal oral mucosa (3%)
Squamos cell carcinoma (86%)
Normal adjacent tissue (4%)
Lung
Small cell lung carcinoma (100%)
Non-small cell carcinoma (78%)
Normal tissue adjacent to tumor (4%)
Breast
Normal breast tissue (0%)
Fibrocystic disease (0%)
Fibroadenoma (28%)
Carcinoma in situ (75%)
Carcinoma, ductal and lobular (88%)
Normal tissue adjacent to tumor (5%)
FNA benign lesions (9%)
FNA malignant lesions (81%)
Hepatic
Normal tissue (0%
Liver Disease, nor
Hepatocellular car
Normal tissue adja
Nor should we forget that telomerase is expressed in over 90% of malignant tumors, another key mechanism in the embryo-fetus, that makes neoplastic cells immortalized.. and that is not due to any DNA mutation ..
strointestinal
stric adenoma (27%)
stric carcinoma (85%)
mal tissue adjacent to tumor (5%)
orectal adenoma (45%)
orectal carcinoma (89%)
mal tissue adjacent to tumor (25%)
Pancreatic carcinoma (95%)
Reproductive Tract - Female
Fetal ovary (100%)
Adult ovary (33%)
Normal endometrium (0%)
Leiomyoma (0%)
Leiomyosarcoma (100%)
Endometrial adenocarcinoma (100%)
Cervical carcinoma (100%)
Vaginal carcinoma (100%)
Ovarian Carcinoma (91%)
Urinary Tract
Normal bladder endothelium (0%)
Dysplastic bladder endothelium (43%)
Bladder carcinoma (92%)
washings (73%)
voided urine (29%)
Renal carcinoma (83%)
Normal tissue adjacent to tumor (0%)
Wilm's tumor (100%)
Normal tissue adjacent to tumor (33%)
Reproductive Tract - male
Testis (100%)
Mature spermatozoa (0%)
Normal prostate (0%)
BPH without carcinoma (5%)
BPH with carcinoma (11%)
High grade PIN (60%)
Prostate carcinoma (90%)
Skin
Normal epidermis (44%)
Squamous cell carcinoma (83%)
Basal cell carcinoma (95%)
Melanoma (86%)

The scientists who adhere to the paradigm of stochastic mutation carcinogenesis (SMT), and more generally **to a linear and gene-centric model of DNA**, have some difficulty to accept this….



Only within a "systemic (olo)genomic" model conceived as a unitary, complex, dynamic, and responsive molecular network, it is possible to suggest that all
epigenetic (*global DNA hypomethylation, hypermethylation of promoter sequences of tumour suppressor genes*),
genetic (*genomic instability, mobilization of transposable sequences*)
and chromosomal (*translocations*) mutations, determining the progression of cancer,
are steps in a (failed or distorted) adaptive and potentially defensive process.

Esteller M. ***Cancer epigenomics*: *DNA methylomes* and *histone-modification maps*** Nat Rev Genet (2007);8(4):286-98; Karpinets TV, Foy BD. ***Tumorigenesis: the adaptation of mammalian cells to sustained stress environment by epigenetic alterations and succeeding matched mutations.*** Carcinogenesis. (2005); 26(8):1323-34; Hauptmann S., Schmitt W.D. ***Transposable elements - Is there a link between evolution and cancer?*** Medical Hypotheses (2006), 66 (3):580-591;



The **"methylation paradox" of cancer cells**.

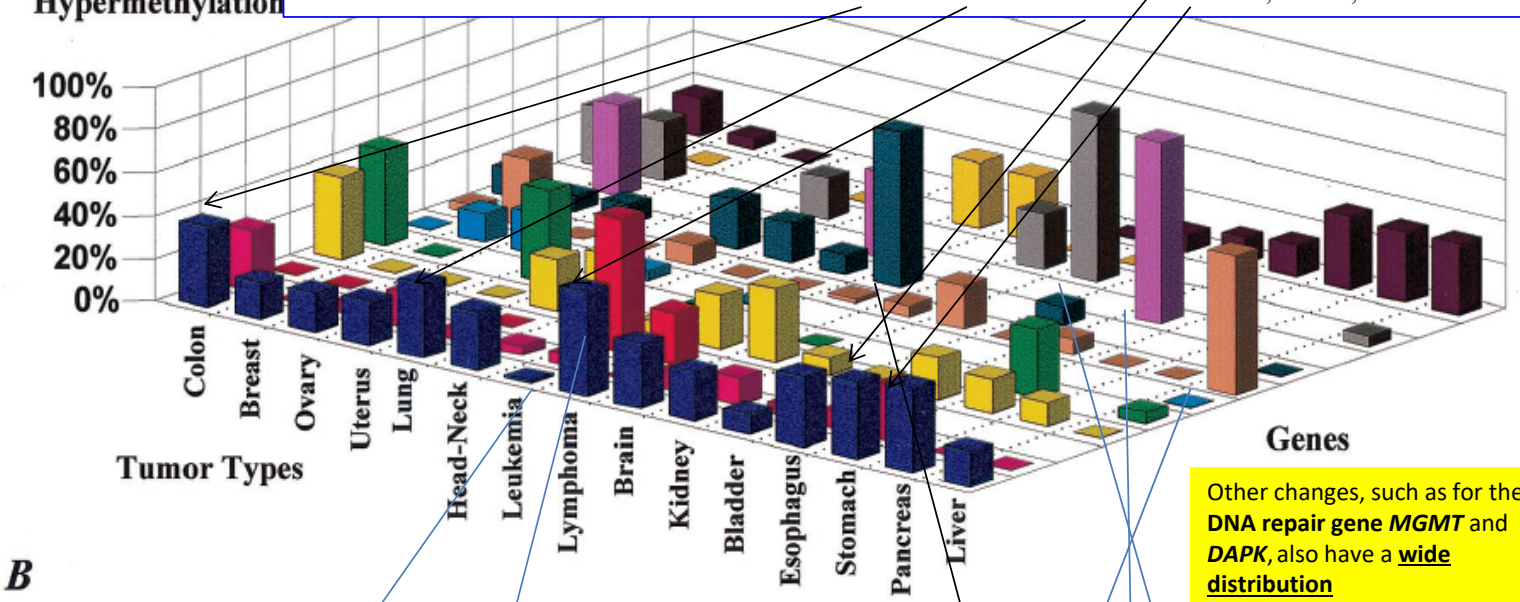
Cancer cells present a **gain of methylated streches at regions that are usually unmethylated (*hypermethylation*)** concomitantly with **loss of methylation at genomic loci that are normally methylated *(global) (hypomethylation),***

Retrosequences activation (Natural Genetic Engineering)

R Villa, F De Santis, A Gutierrez, S Minucci, PG Pelicci, L Di Croce ***Epigenetic gene silencing in acute promyelocytic leukemia*** Biochem Pharmacol (2004) 68: 1247-54

ONE OR MORE OF THE GENES STUDIED IS HYPERMETHYLATED IN EVERY TUMOR TYPE. HOWEVER, **THE PROFILE OF PROMOTER HYPERMETHYLATION FOR THE GENES DIFFERS FOR EACH CANCER TYPE, PROVIDING A TUMOR-TYPE AND GENE-SPECIFIC PROFILE** (EVEN IF SOME GENES, SUCH AS THE CELL CYCLE INHIBITOR P16INK4A, ARE HYPERMETHYLATED ACROSS MANY TUMOR TYPES INCLUDING COLORECTAL, LUNG, AND BREAST CARCINOMAS))

A



Other changes, such as for the **DNA repair gene *MGMT*** and ***DAPK***, also have a **wide distribution**

B

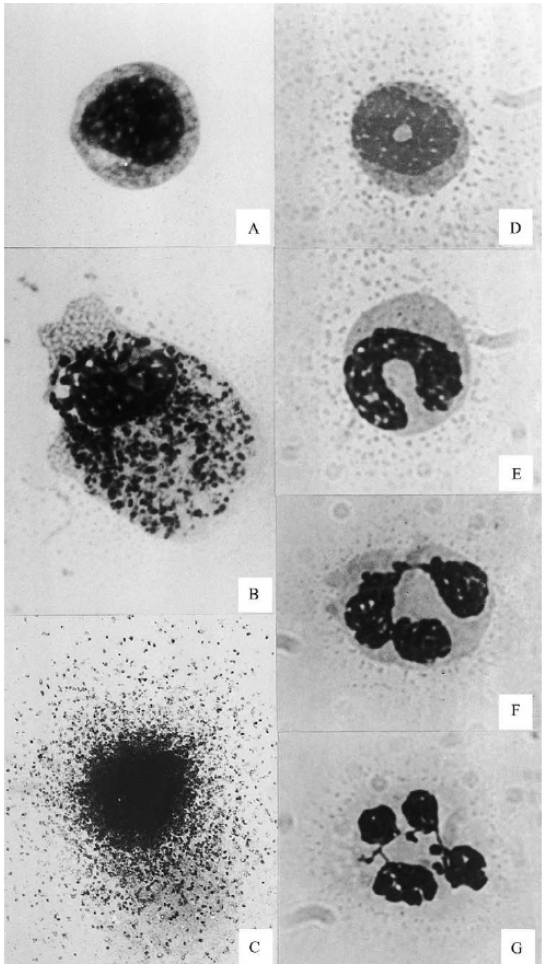
	p16 INK4a	*p14 ARF*	*p15 INK4b*	*MGMT*	*hMLH1*	*BRCA1*	*GSTP1*	*DAPK*	*CDH1*	*TIMP-3*	*p73*	*APC*
Colon	37%,41/110	28%,37/132	0%,0/19	39%,127/323	44%,15/34*	0%,0/18	4%,1/23	13%,2/23	N.D.	27%,6/22	0%,0/10	18%,20/108
Breast	17%,11/66	0%,0/20	0%,0/16	0%,0/36	0%,0/10	13%,11/84	31%,24/77	7%,1/15	42%,37/88	27%,8/29	0%.0/15	5%,1/19
Ovary	18%,4/22	5%,1/20	N.D.	0%,0/23	N.D.	19%,11/58	0%,0/10	9%,2/23	N.D.	N.D.	N.D.	0%,0/20
Uterus	20%,6/29	16%,4/25	N.D.	0%,0/17	43%,24/56*	N.D.	0%,0/20	N.D.	N.D.	N.D.	N.D.	N.D.
Lung	31%,28/89	6%,4/62	0%,0/21	21%,18/83	0%,0/20	4%,1/22	9%,2/21	16%,10/64	N.D.	19%,4/21	0%,0/22	0%,0/17
Head-Neck	27%,26/95	4%,1/25	N.D.	32%,37/116	N.D.	N.D.	0%,0/106	18%,17/92	N.D.	N.D.	N.D.	0%,0/10
Leukemia	1%,1/150	5%,1/20	62%,93/150	6%,2/31	6%,3/51	0%,0/19	0%,0/10	9%,8/86	40%,30/75	N.D.	31%,11/35	N.D.
Lymphoma	48%,12/25	0%,0/22	24%,6/25	25%,15/61	N.D.	N.D.	2%,1/47	72%,21/29	N.D.	N.D.	30%,3/10	N.D.
Brain	30%,3/10	9%,2/22	N.D.	34%,74/213	0%,0/15	N.D.	5%,1/20	N.D.	N.D.	26%,20/77	0%,0/22	0/10
Kidney	23%,6/25	13%,5/38	N.D.	8%,1/12	N.D.	N.D.	20%,8/35	N.D.	N.D.	78%,28/36	0%,0/10	8%,1/12
Bladder	9%,1/11	5%,1/20	N.D.	4%,2/44	N.D.	N.D.	0%,0/24	9%,1/11	N.D.	N.D.	N.D.	10%,2/19
Esophagus	33%,5/15	8%,3/37	N.D.	20%,3/14	N.D.	N.D.	7%,1/14	N.D.	84%,26/31	N.D.	N.D.	15%,4/27
Stomach	36%,8/22	26%,31/118	N.D.	16%,10/60	32%,21/65*	N.D.	0%,0/22	N.D.	N.D.	N.D.	N.D.	34%,13/38
Pancreas	39%,7/18	0%,0/20	N.D.	11%,2/18	N.D.	N.D.	0%,0/18	N.D.	N.D.	N.D.	N.D.	33%,6/18
Liver	15%,3/20	0%,0/20	N.D.	0%,0/59	5%,2/20	0%,0/18	65%,13/20	0%,0/20	N.D.	5%,1/20	N.D.	33%,6/18

seminars in CANCER BIOLOGY, Vol. 12, 2002: pp. 339–346
doi:10.1016/S1044–579X(02)00054-8, available online at http://www.idealibrary.com on IDEAL®

Epigenetics wins over genetics: induction of differentiation in tumor cells

*Joseph Lotem and Leo Sachs**

Malignant cells are genetically abnormal, but can the malignant phenotype revert to a non-malignant phenotype without correcting these genetic abnormalities? It has been found that this reversion can be achieved by reprogramming tumor cells by epigenetic changes induced by differentiation. The epigenetic suppression of malignancy by inducing differentiation bypasses the genetic abnormalities in tumor cells. Studies with myeloid leukemic cells have shown that some leukemic cells can be induced to differentiate by cytokines that control normal hematopoiesis, and that myeloid leukemic cells resistant to normal cytokines can be induced to differentiate by compounds that use alternative differentiation pathways. The epigenetic reprogramming of tumor cells by inducing differentiation has also been found with other types of tumors and can be used for tumor therapy. By this reversion of the malignant to non-malignant phenotype, epigenetics wins over genetics.



On these bases **for over 20 years it has been known that it is possible, in certain situations, to act on cancer cells and even on some neoplasms by means of epigenetic factors capable of reverting the neoplastic phenotype** (and even the ***carcinogenic molecular mechanisms***)..

COMMENTARY

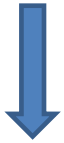
Reprogramming cancer cells: back to the future

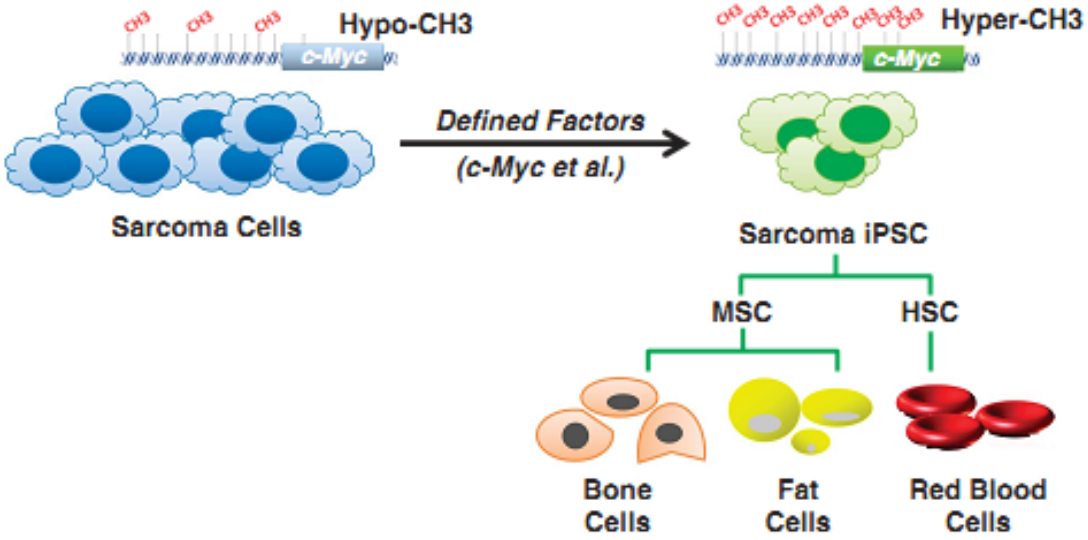
J-Y Lang, Y Shi and YE Chin

Reprogramming healthy somatic cells into induced pluripotent stem cells (iPSCs) with four defined factors (*Oct4, Sox2, c-Myc* and *Klf4*) has been intensively investigated. However, reprogramming diseased cells such as cancer cells has fallen much behind. In this issue of *Oncogene*, Zhang *et al.* demonstrated that reprogrammed sarcoma cells with defined factors, as well as *Nanog* and *Lin28*, lost their tumorigenicity and dedifferentiated to mesenchymal stem cells (MSC) and hematopoietic stem cell (HSC)-like cells that can be terminally differentiated into mature connective tissues and red blood cells, suggesting sarcoma cells may be reversed back to a stage of common ancestor iPSC bifurcating for HSC and MSC ontogeny. It may, therefore, provide a novel strategy for cancer treatment via ancestor pluripotency induction

Oncogene (2013) **32,** 2247–2248; doi:10.1038/onc.2012.349; published online 6 August 2012

These **cellular reprogramming strategies** are now proven to be **effective in cancer, both experimentally… and clinically**





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Biochemical Pharmacology 68 (2004) 1247–1254
Biochemical Pharmacology
www.elsevier.com/locate/biochempharm

Epigenetic gene silencing in acute promyelocytic leukemia

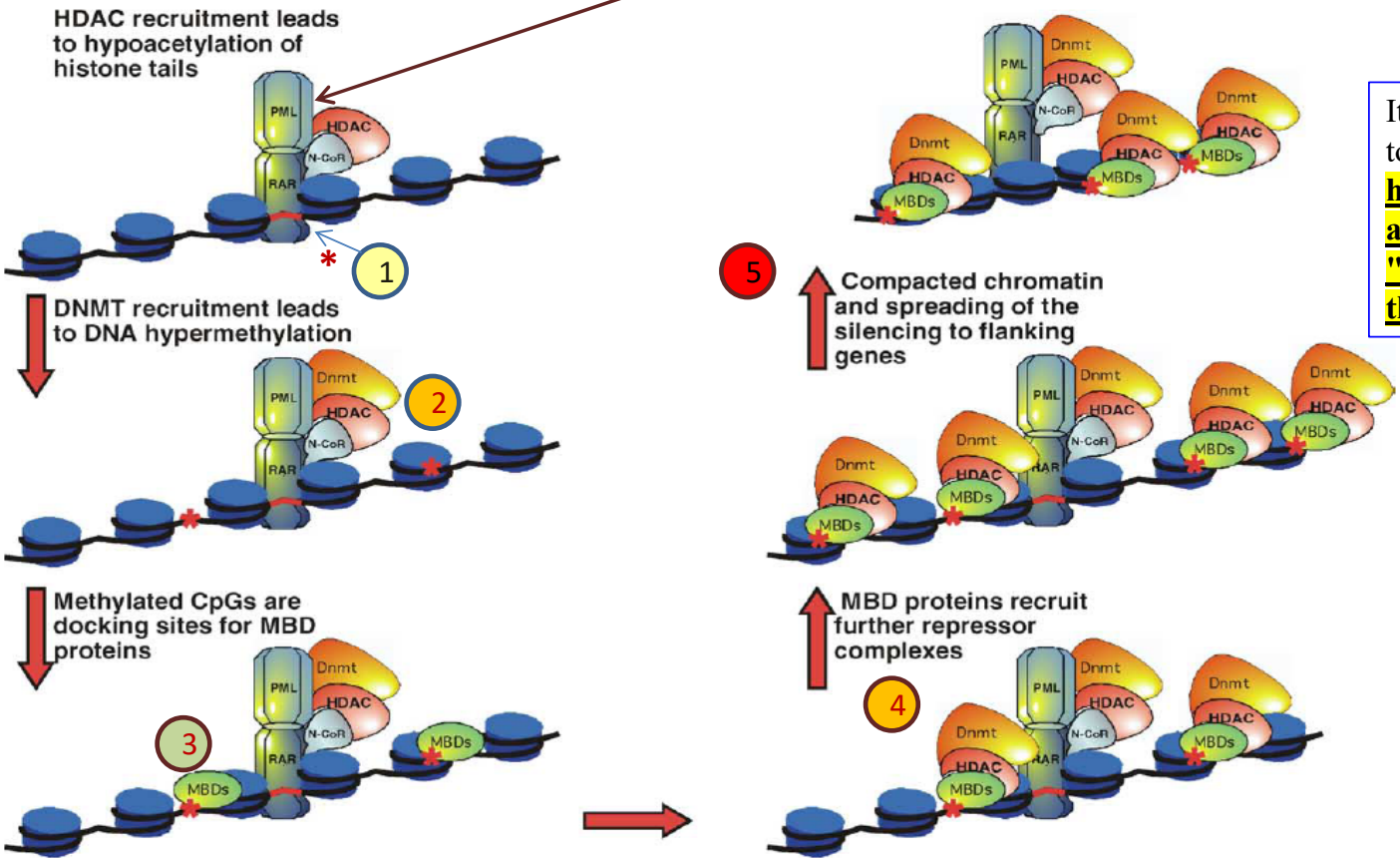
R. Villa[a], F. De Santis[b], A. Gutierrez[a], S. Minucci[b], P.G. Pelicci[b], L. Di Croce[a,c,*]

[a]*Center for Genomic Regulation, Passeig Maritim 37-49, 08003 Barcelona, Spain*
[b]*European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy*
[c]*ICREA and Center for Genomic Regulation, Passeig Maritim 37-49, 08003 Barcelona, Spain*

Particularly in certain forms of **acute infantile leukemia with poor prognosis, such as promyelocytic leukemia,** in which PML-RAR a as well as other **leukemia-associated fusion proteins change the chromatin structure** (specifically, aberrant recruitment of different chromatin modifying enzymes to specific promoters induce **DNA hypermethylation and heterochromatin formation leading to transcriptional silencing of some key-genes)**

nscription has highlighted the importance of
c changes—in particular, aberrant promoter
hypermethylation that is associated with inappropriate gene silencing—affect virtually every step in tumor progression. Intriguingly, methylation patterns are severely altered in tumors, with an overall hypomethylation of the genome and hypermethylation of islands of CpGs clusters within specific DNA regions. Though overexpression of DNA methyltransferases (DNMTs) has been proposed to be a mechanism for aberrant genome methylation, it does not explain the specific regional hypermethylation in cancer cells. We have analyzed the role of chromatin modifying activities in cell transformation using acute promyelocytic leukemia as a model system. This disease is caused by expression of the PML-RARα fusion protein, thus offering the opportunity of studying the mechanisms of leukemogenesis through molecular investigation of the activity of the directly transforming protein. Recent evidence suggests that PML-RARα as well as other leukemia-associated fusion proteins induce changes in the chromatin structure. Specifically, aberrant recruitment of different chromatin modifying enzymes to specific promoters induces DNA hypermethylation and heterochromatin formation, which consequentially leads to the transcriptional silencing of that genes. Importantly, these epigenetic modifications were found to contribute to the leukemogenic potential of PML-RARα. These observations suggest that epigenetic alterations could actively contribute to the development of APL and other hyperproliferative diseases.

Schematic representation of the **step-wise silencing** of **PML-RARα** target genes



It is important to remember that today, **promyelocytic leukemia heals with retinoic acid, which acts epigenetically by "releasing" the genes blocked by the PML-RARa fusion protein..**

1 The **oncoprotein** **PML-RARα** recognizes a well-defined **DNA sequence** *

2 .. recruits **repressor enzymes**, such as **HDACs** and **DNMTs** leading to **hypo-acetylation of histone tails, DNA methylation,** and **transcriptional silencing…**

3 **Methylated CpGs** are potential **docking sites for MBD proteins**, which can in turn **recruit further repressor enzymes**. 4

5 The **progression wave..** might ‘‘close’’ the chromatin structure and **could even influence neighboring genes**.

ANTIOXIDANTS & REDOX SIGNALING
Volume 21, Number 10, 2014

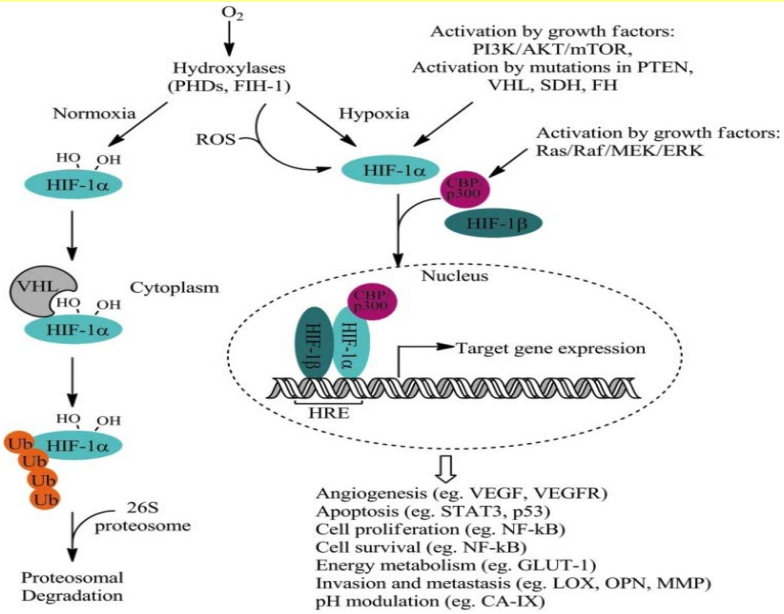
DOI: 10.1089/ars.2013.5378

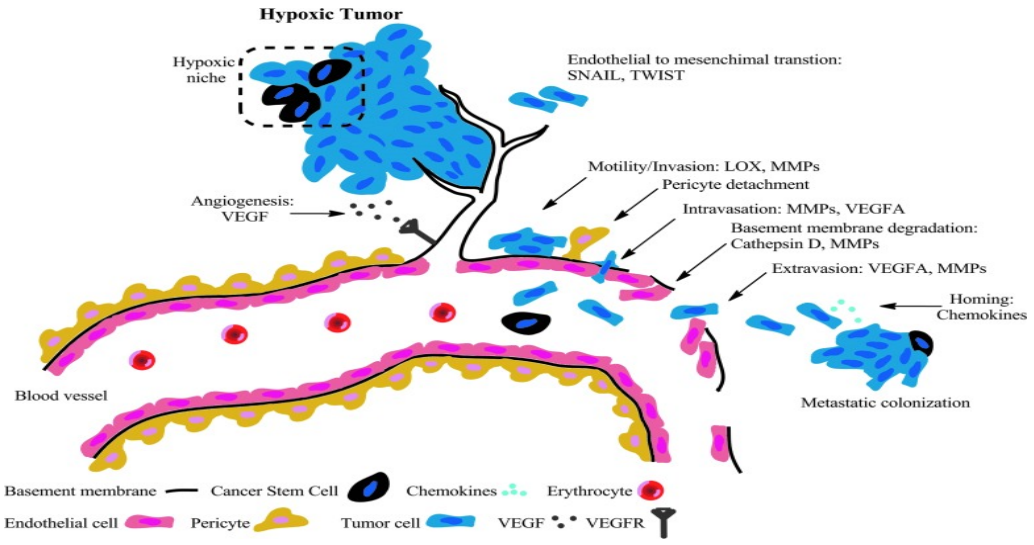
COMPREHENSIVE INVITED REVIEW

The Clinical Importance of Assessing Tumor Hypoxia: Relationship of Tumor Hypoxia to Prognosis and Therapeutic Opportunities

Joseph C. Walsh,[1] Artem Lebedev,[1] Edward Aten,[2] Kathleen Madsen,[3] Liane Marciano,[2] and Hartmuth C. Kolb[1]

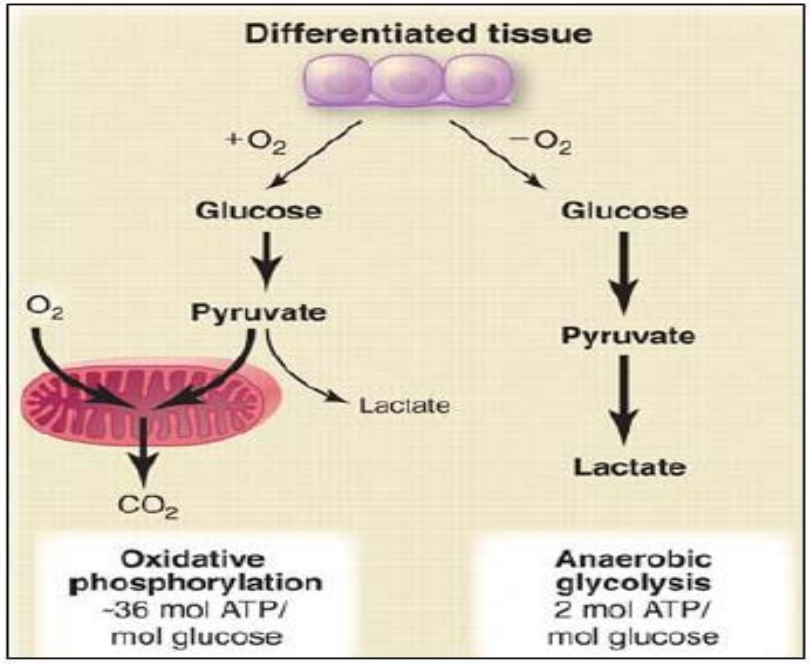
I **tumori ipossici** accumulano e propagano le **cellule staminali tumorali**, aumentando il **rischio di metastasi** e **riducendo l'efficacia dell'intervento chirurgico, della chemioterapia e della chemio-radioterapia**

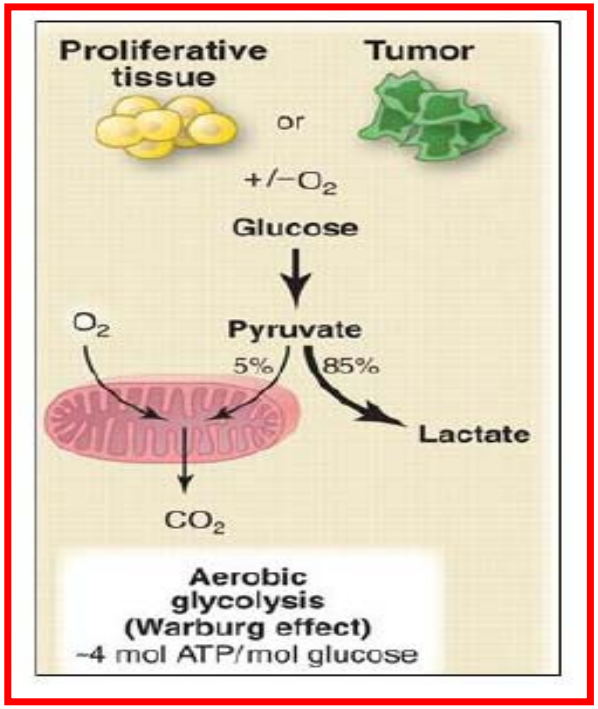




Effetto Warburg.

Warburg nel 1921 dimostrò che le cellule tumorali esibiscono una inusuale richiesta di glucosio con concomitante alta produzione di acido lattico, pur in presenza di ossigeno, per **attivazione preferenziale dell' «ancestrale» glicolisi aerobica**

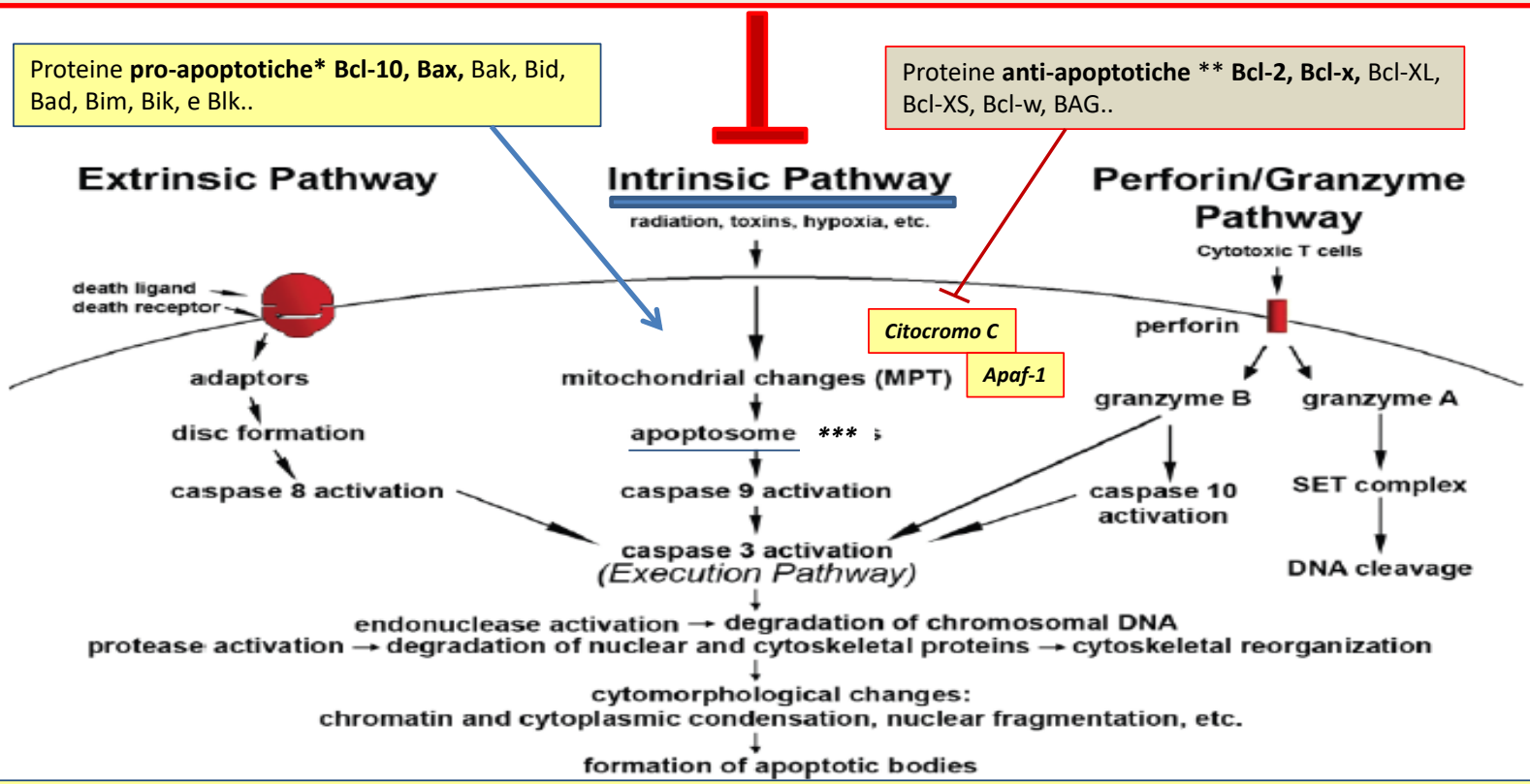




Le **cellule normali/non cancerose metabolizzano il prodotto finale della via glicolitica, il piruvato, nei mitocondri**, attraverso il **ciclo di Krebs e la fosforilazione ossidativa**, *pathway* metabolico particolarmente vantaggioso dal punto di vista energetico poiché porta alla produzione di **36 molecole di ATP per molecola di glucosio metabolizzata**

Le **cellule tumorali**, invece, **inibiscono la completa ossidazione mitocondriale del piruvato, il quale viene preferenzialmente convertito in lattato** dalla ***Lattato deidrogenasi (LDH)*.**

Inoltre la trasformazione verso un **fenotipo glicolitico determina resistenza al processo di morte cellulare programmata (apoptosi):** molti **enzimi coinvolti nella glicolisi tra cui *l'esochinasi (HK),* sono infatti anche importanti regolatori dell'apoptosi.**



Il **controllo e la regolazione degli eventi apoptotici** mediati dai ***mitocondri*** avviene attraverso i membri della **famiglia di proteine (pro* e anti-apoptotiche **) Bcl-2** per la cui regolazione la **proteina p53** svolge un ruolo chiave.

Le 3 principali *pathways* apoptotiche. La ***via intrinseca*** «mitocondriale» implica una corretta funzionalità dei mitocondri ed è di norma innescata da una vasta gamma di stimoli che producono segnali intracellulari e causano **cambiamenti nella membrana mitocondriale interna.** Tali cambiamenti si traducono nell'apertura del **poro di transizione della permeabilità mitocondriale (MPT)**, nella perdita del **potenziale di membrana del mitocondrio e nel rilascio, nel citosol, di proteine pro-apoptotiche, di norma sequestrate nello spazio intermembrana mitocondriale , tra cui il *citocromo C*** che, una volta liberato nel citosol, forma un **complesso con *Apaf-1 (apoptotic protease activating factor)*** e con la ***pro-caspasi-9 (apoptosoma)****** e sucessiva attivazione delle ***caspasi effettrici*** (la -**3**, la -6 e la -7 → e della ***final common pathway*** (appunto comune a tutte le vie apoptotiche)

Ma perché **le cellule tumorali, altamente proliferanti e richiedenti energia, dipendono dalla glicolisi aerobia piuttosto che dall'ossidazione del glucosio**, energeticamente più vantaggiosa?

nature reviews cancer

Robert A. Gatenby ✉ & Robert J. Gillies

Nature Reviews Cancer **4**, 891–899(2004)

WHY DO CANCERS HAVE HIGH AEROBIC GLYCOLYSIS?

Robert A. Gatenby and Robert J. Gillies‡*

Abstract | If carcinogenesis occurs by somatic evolution, then common components of the cancer phenotype result from active selection and must, therefore, confer a significant growth advantage. A near-universal property of primary and metastatic cancers is upregulation of glycolysis, resulting in increased glucose consumption, which can be observed with clinical tumour imaging. We propose that persistent metabolism of glucose to lactate even in aerobic conditions is an adaptation to intermittent hypoxia in pre-malignant lesions. However, upregulation of glycolysis leads to microenvironmental acidosis requiring evolution to phenotypes resistant to acid-induced cell toxicity. Subsequent cell populations with upregulated glycolysis and acid resistance have a powerful growth advantage, which promotes unconstrained proliferation and invasion.

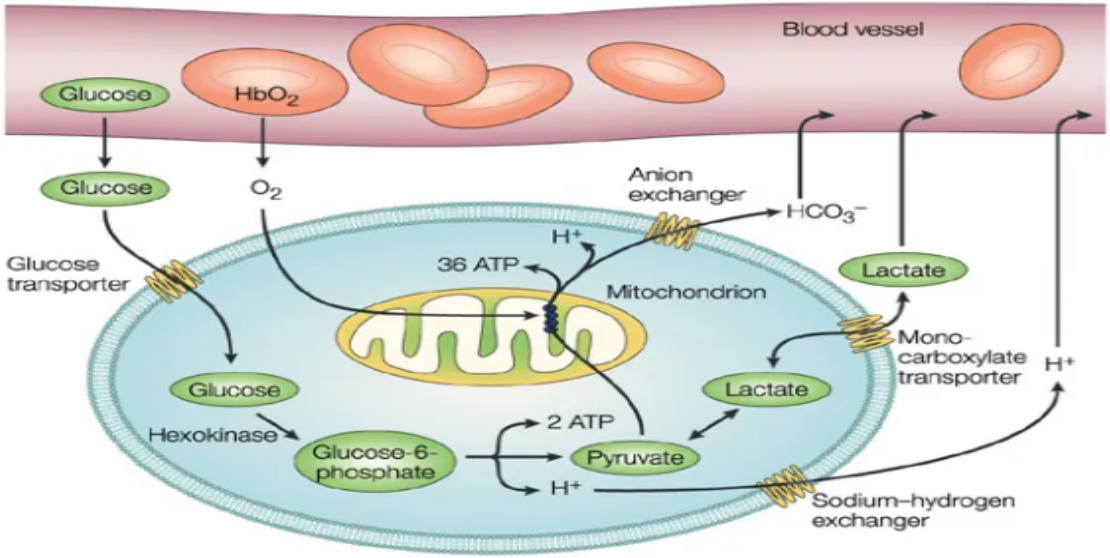
L'upregolazione costitutiva della glicolisi è probabilmente un **adattamento all'ipossia** che si sviluppa nelle **lesioni pre-neoplastiche.**

La **sovraregolazione della glicolisi** provoca ***acidosi microambientale*** e richiede un ulteriore adattamento attraverso **l'evoluzione somatica di fenotipi resistenti alla tossicità indotta dall'acidosi**

Le popolazioni cellulari che emergono da questa sequenza hanno un forte vantaggio evolutivo, poiché il **micro-ambiente diviene tossico per le cellule normali**, ma innocuo per se stesse. L'acidosi ambientale facilita l'invasione attraverso la distruzione di popolazioni normali adiacenti, il degrado della matrice extracellulare e la promozione dell'angiogenesi..

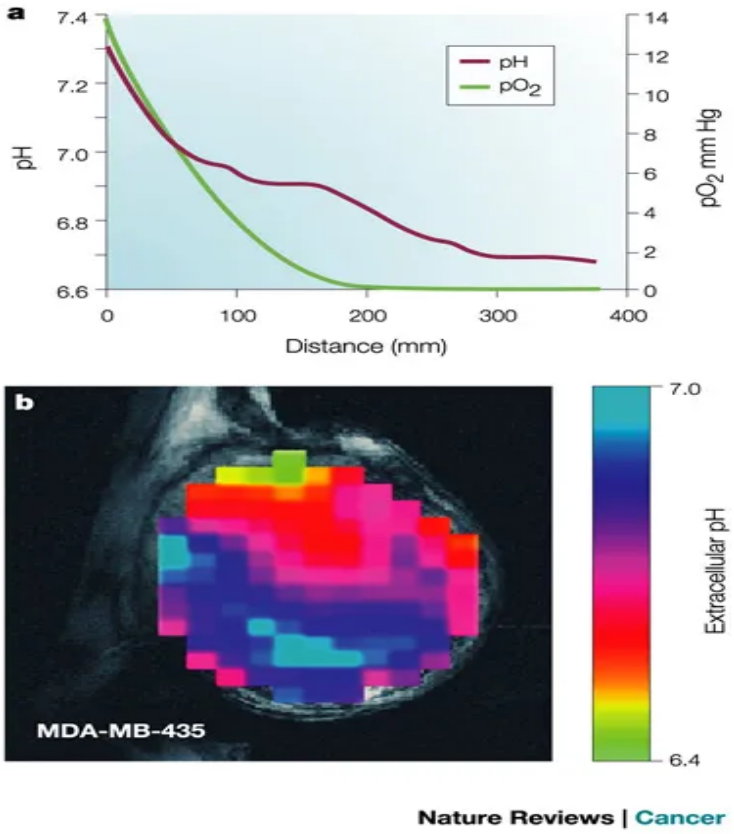
Secondo Gatenby e Gillies , **all'inizio della carcinogenesi le cellule trasformate si affidano alla sola glicolisi anaerobica per la produzione di ATP, poiché si trovano in un microambiente ipossico**. In queste condizioni viene **attivato il fattore ipossico HIF-1** che promuove l'espressione di diversi **trasportatori del glucosio** e di enzimi, quali la ***piruvato deidrogenasi chinasi (PDK)*** che **inibisce il complesso multienzimatico della piruvato deidrogenasi (PDH), responsabile della conversione del piruvato in acetil-CoA, limitando così l'ingresso del piruvato nel ciclo dell'acido citrico e quindi la sua ossidazione a livello mitocondriale** (20).

Figura 1: metabolismo del glucosio nelle cellule di mammifero.



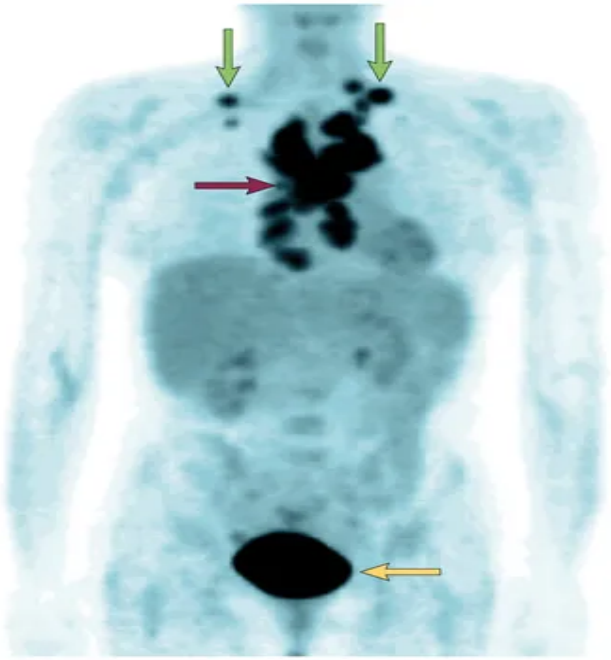
Il sangue afferente fornisce glucosio e ossigeno (sull'emoglobina) ai tessuti, dove raggiunge le cellule per diffusione. Il glucosio viene assorbito da specifici trasportatori, dove viene prima convertito in glucosio-6-fosfato da esocinasi e poi in piruvato, generando 2 ATP per glucosio. In presenza di ossigeno, il piruvato viene ossidato a HCO_3, generando 36 ATP aggiuntivi per glucosio. In assenza di ossigeno, il piruvato viene ridotto a lattato, che viene esportato dalla cellula. Si noti che entrambi i processi producono ioni idrogeno (H^+), che causano l'acidificazione dello spazio extracellulare. HbO

Figura 4: iperacidità dei tumori.



I prodotti metabolici della glicolisi, come gli ioni idrogeno (H^+), causano **un'acidificazione spazialmente eterogenea** ma coerente dello spazio extracellulare, che sembra provocare una **tossicità cellulare «selettiva»**

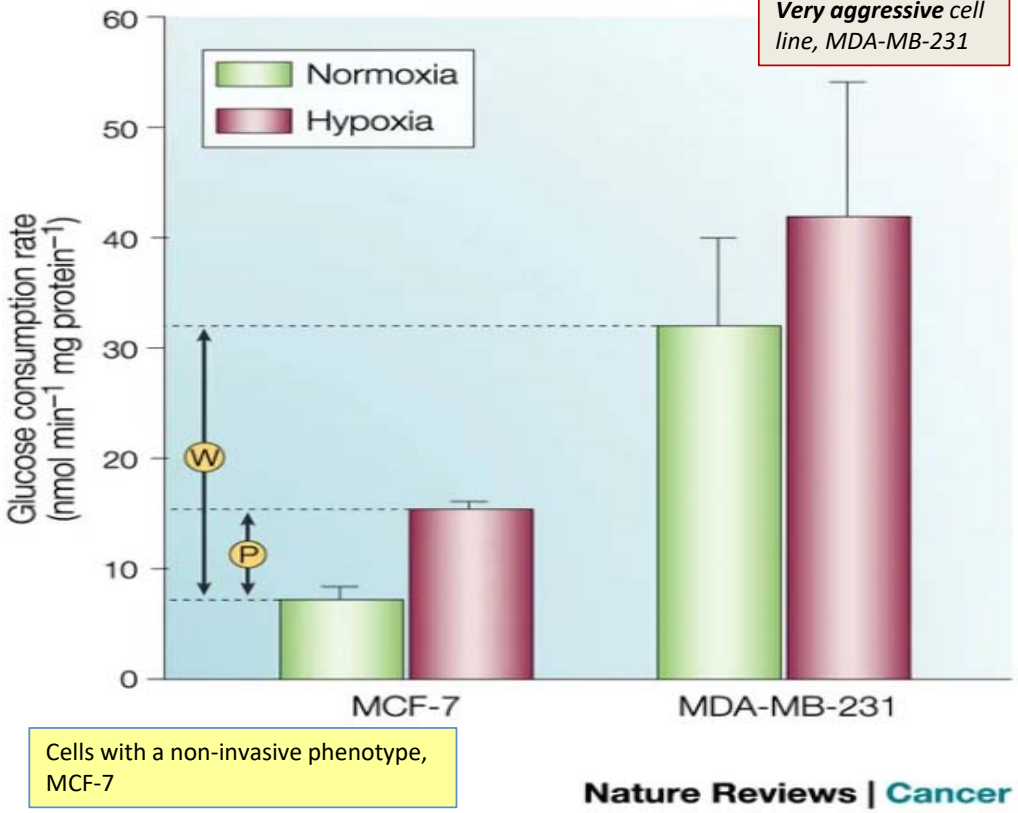
Figura 2: Tomografia a emissione di positroni con ^{18} fluorodeossiglucosio di un paziente con linfoma.



Nature Reviews | Cancer

I nodi mediastinici (freccia viola) e nodi sopraclaveari (frecce verdi) mostrano un elevato assorbimento di ^{18} fluorodeossiglucosio (FdG), dimostrando che i tumori in questi nodi hanno alti livelli di assorbimento di FdG. Anche la vescica (freccia gialla) ha un'alta attività, a causa dell'escrezione del radionuclide.

Figura 3: effetti di Pasteur e Warburg nelle linee cellulari non invasive e metastatiche del carcinoma mammario.



***Very aggressive** cell line, MDA-MB-231*

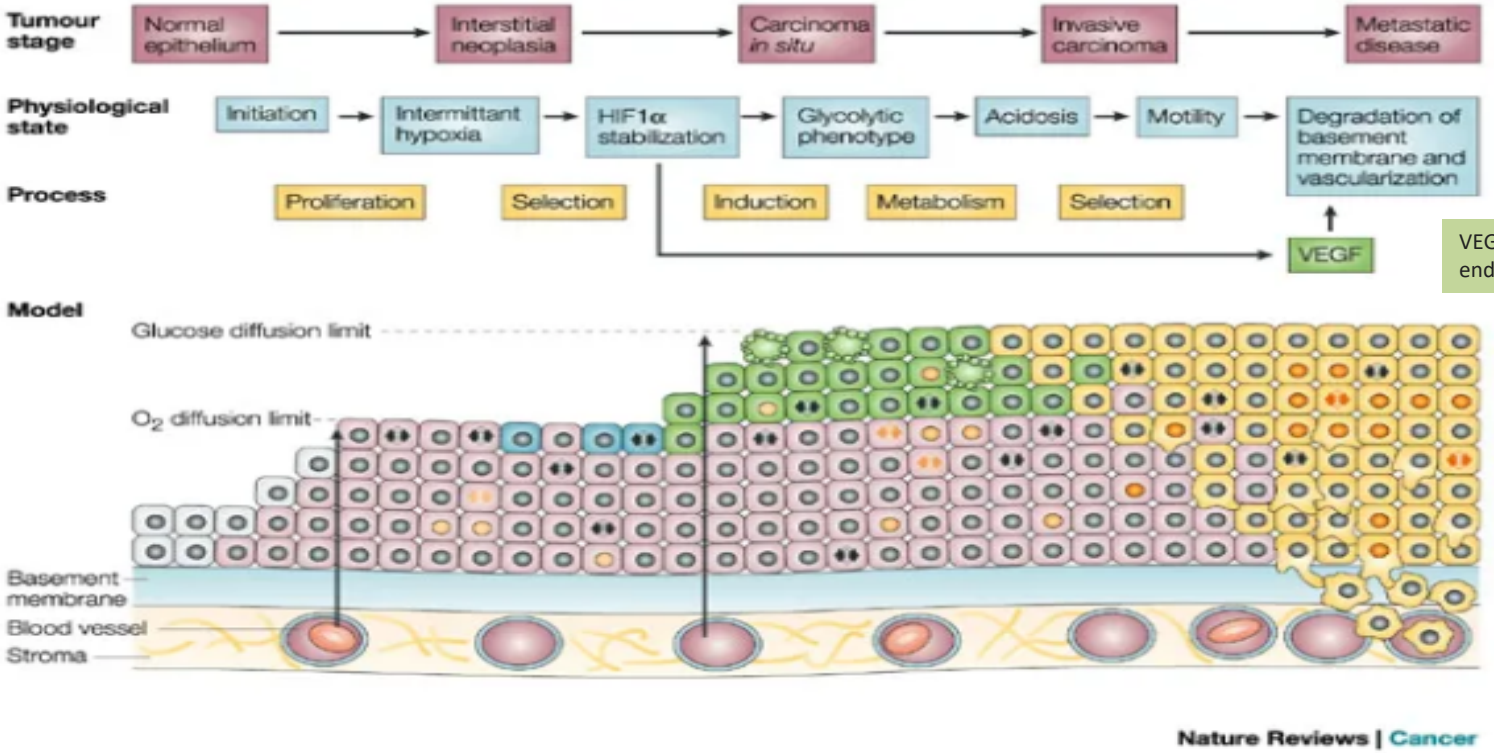
Cells with a non-invasive phenotype, MCF-7

Nature Reviews | Cancer

In entrambe le linee cellulari, il consumo di glucosio è ridotto in presenza di ossigeno - l'effetto Pasteur (P). Tuttavia, la linea cellulare più aggressiva, MDA-MB-231, ha un consumo di glucosio molto più elevato in presenza di ossigeno rispetto alle cellule MCF-7 con un fenotipo non invasivo: l'effetto Warburg (W). Ciò è coerente con le scansioni tomografiche ad emissione di positroni con ^{18} fluorodeossiglucosio, che mostrano che un maggiore assorbimento di glucosio è correlato a fenotipi più aggressivi e risultati clinici più scarsi.

Figura 6: Modello per le interazioni cellula-ambiente nella carcinogenesi.

HIF1α, fattore 1-inducibile dall'ipossia



VEGF, fattore di crescita endoteliale vascolare

Gli stadi della crescita del tumore e i loro stati fisiologici associati sono schematizzati, dimostrando che la progressione da uno stadio all'altro è governata da processi collettivi. **Le cellule epiteliali normali (grigie) diventano iperproliferative (rosa) dopo l'induzione**. Quando raggiungono il limite di diffusione dell'ossigeno, **diventano ipossici (blu), il che può portare alla morte cellulare (cellule apoptotiche mostrate con blebbing) o all'adattamento di un fenotipo glicolitico (verde),** che consente alle cellule di sopravvivere. Come conseguenza della glicolisi, **le lesioni diventano acidotiche e selezionano le cellule mobili (gialle) che alla fine violano la membrana basale e le mutazioni nelle cellule aumentano (nuclei mostrati come arancione chiaro per una mutazione e arance più scure per più mutazioni).**

Stem Cell Reports
Article
OPEN ACCESS

Glycolysis Regulates Human Embryonic Stem Cell Self-Renewal under Hypoxia through HIF-2α and the Glycolytic Sensors CTBPs

Sophie A. Arthur,[1] Jeremy P. Blaydes,[2,*] and Franchesca D. Houghton[1,*]
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https://doi.org/10.1016/j.stemcr.2019.02.005

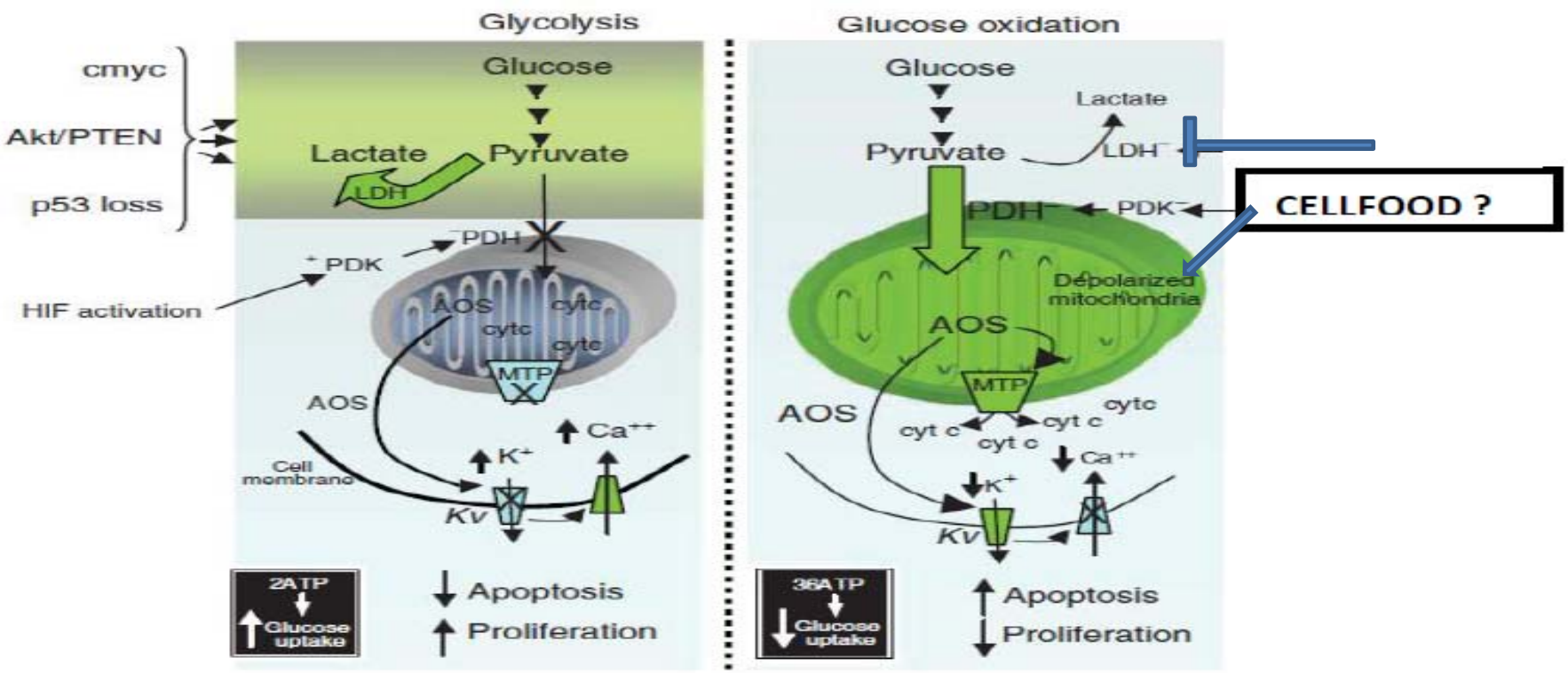
L'ipossia supporta la pluripotenza, riducendo la normale tendenza del hESCs a differenziarsi!

hESCs are particularly difficult to maintain in culture, due to their tendency to spontaneously differentiate, suggesting that standard culture conditions at atmospheric, 20% oxygen tension are sub-optimal. It is now widely recognized that culturing hESCs at a lower oxygen tension is advantageous for their maintenance, in terms of reduced spontaneous differentiation, improved proliferation, and increased expression of key pluripotency markers (Chen et al., 2010; Ezashi et al., 2005; Forristal et al., 2010; Ludwig et al., 2006; Prasad et al., 2009; Westfall et al., 2008); an effect mediated by hypoxia-inducible factors (HIFs).

Le **cellule staminali embrionali umane (hESC)** sono difficili da mantenere in cultura, a causa della loro **tendenza a differenziarsi spontaneamente**..
coltivare **hESC ad una tensione di ossigeno inferiore** è vantaggioso per il loro mantenimento, in termini di **ridotta differenziazione spontanea,** maggior **proliferazione** e **massima espressione dei marcatori di pluripotenza: effetti mediati dai fattori inducibili dall'ipossia.** Pertanto, **l'ipossia supporta la pluripotenza mantenendo la glicolisi**, che sostiene i maggiori bisogni energetici della cellula

CELLFOOD® **SHIFTAGGIO DALLA VIA GLICOLITICA** A QUELLA **MITOCONDRIALE/OSSIDATIVA**

Nelle **linee tumorali trattate** è stata osservata **una riduzione dell'attività dell'enzima LDH e della quantità di lattato rilasciato nell'ambiente extracellulare** rispetto alle cellule non trattate



Inoltre CELLFOOD® si è dimostrato in grado di inibire il fattore ipossico HIF-1 che svolge un ruolo chiave nella regolazione del fenotipo glicolitico e di **ridurre l'espressione del trasportatore di membrana GLUT-1..**

E' dunque possibile ipotizzare che CELLFOOD® favorisca la riattivazione della via ossidativa mitocondriale, rendendo in questo modo la cellula tumorale suscettibile all'apoptosi

Associazione Italiana di Oncologia Medica

PROGETTO AMBIENTE E TUMORI

Coordinatore Ruggero Ridolfi

Edito da Aiom - Associazione Italiana di Oncologia Medica
Edizione 2011

Associazione Italiana di Oncologia Medica

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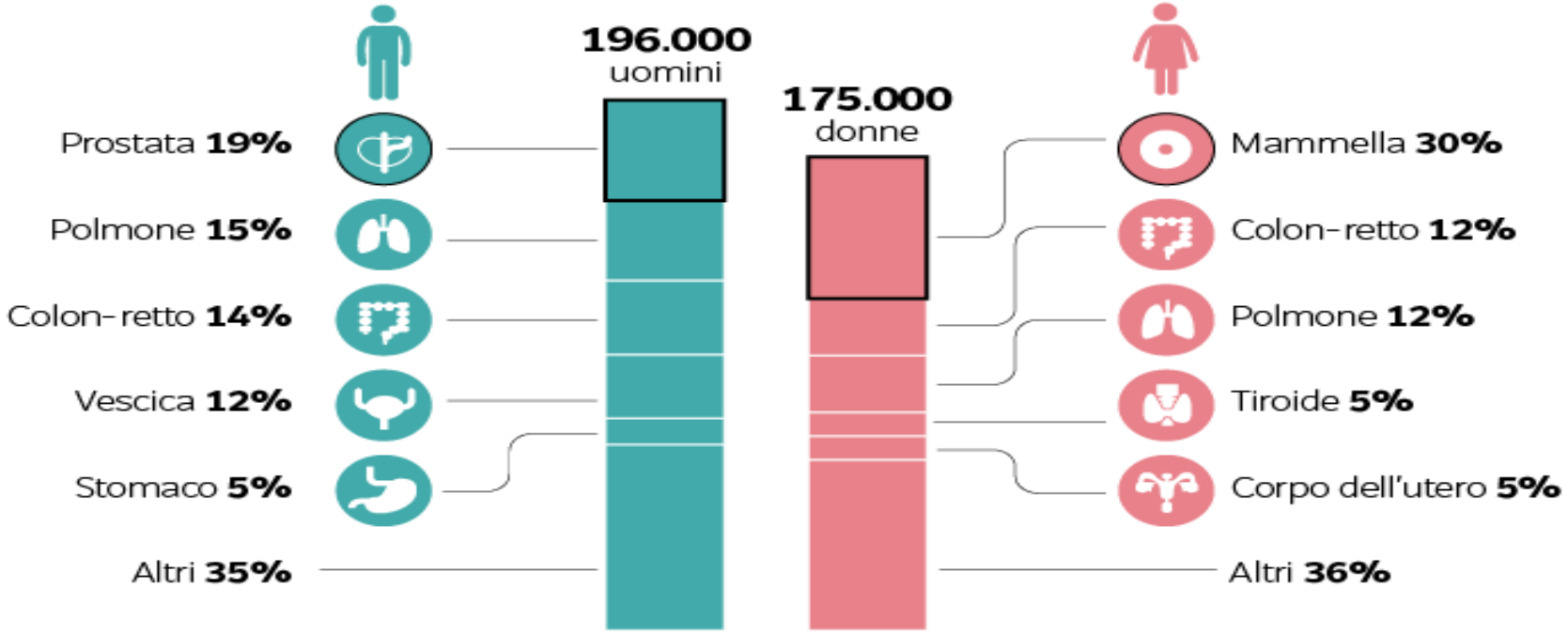
Francesco Boccardo – Genova (Past President AIOM)
e tutto il Consiglio Direttivo AIOM

Telefoni cellulari e tumori al cervello: cosa dicono 20 anni di ricerche

di **Milena Gabanelli e Simona Ravizza**

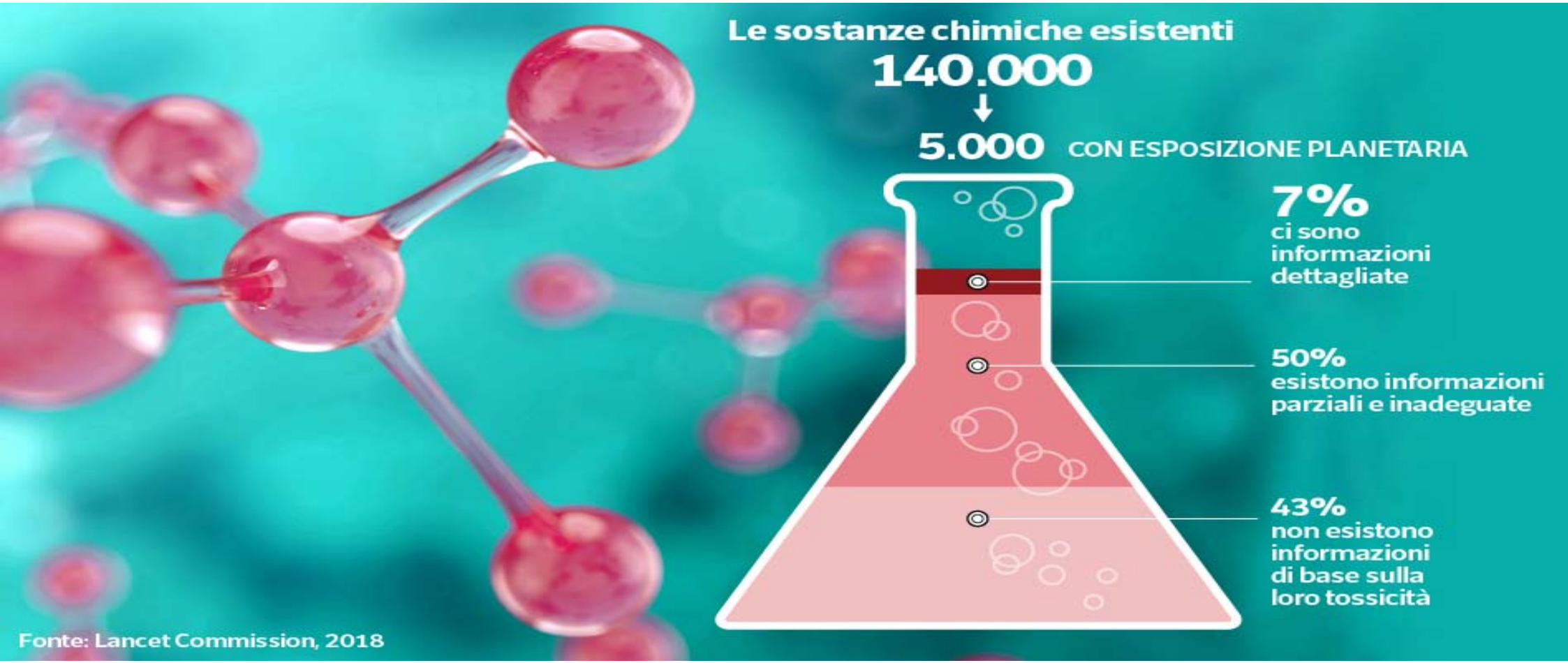
I nuovi casi del tumore maligno nel 2019

371.000



COSA PUÒ PROVOCARE I TUMORI

Fonte: Aiom 2019


Le sostanze chimiche esistenti
140.000
5.000 CON ESPOSIZIONE PLANETARIA
7%
ci sono informazioni dettagliate
50%
esistono informazioni parziali e inadeguate
43%
non esistono informazioni di base sulla loro tossicità
Fonte: Lancet Commission, 2018

I fattori di rischio

AGENTI CHIMICI E COMPOSTI

Formaldeide

Leucemie
Nasofaringe

Benzene

Leucemie

ESPOSIZIONE LAVORATIVA

Alluminio

Polmone
Vie urinarie

Alcol isopropilico

Cavità nasali
Seni paranasali

METALLI

Cromo

Polmone

Nichel

Polmone
Cavità nasali
Seni paranasali

POLVERI E FIBRE

Amianto

Laringe
Polmone
Mesotelioma
Ovai

Polveri di cuoio e di legno

Cavità nasali
Seni paranasali

RADIAZIONI

Radon 222

Polmone

Radio 226 e radio 228

Osso
Processo mastoide
Seni paranasali

Fonte: Rapporto Aiom 2019, Agenti cancerogeni per l'uomo e relativi tumori associati. IARC, 2011

Raccomandazioni sull'uso dei telefonini

Non tenerlo appoggiato all'orecchio ma almeno a 5 cm

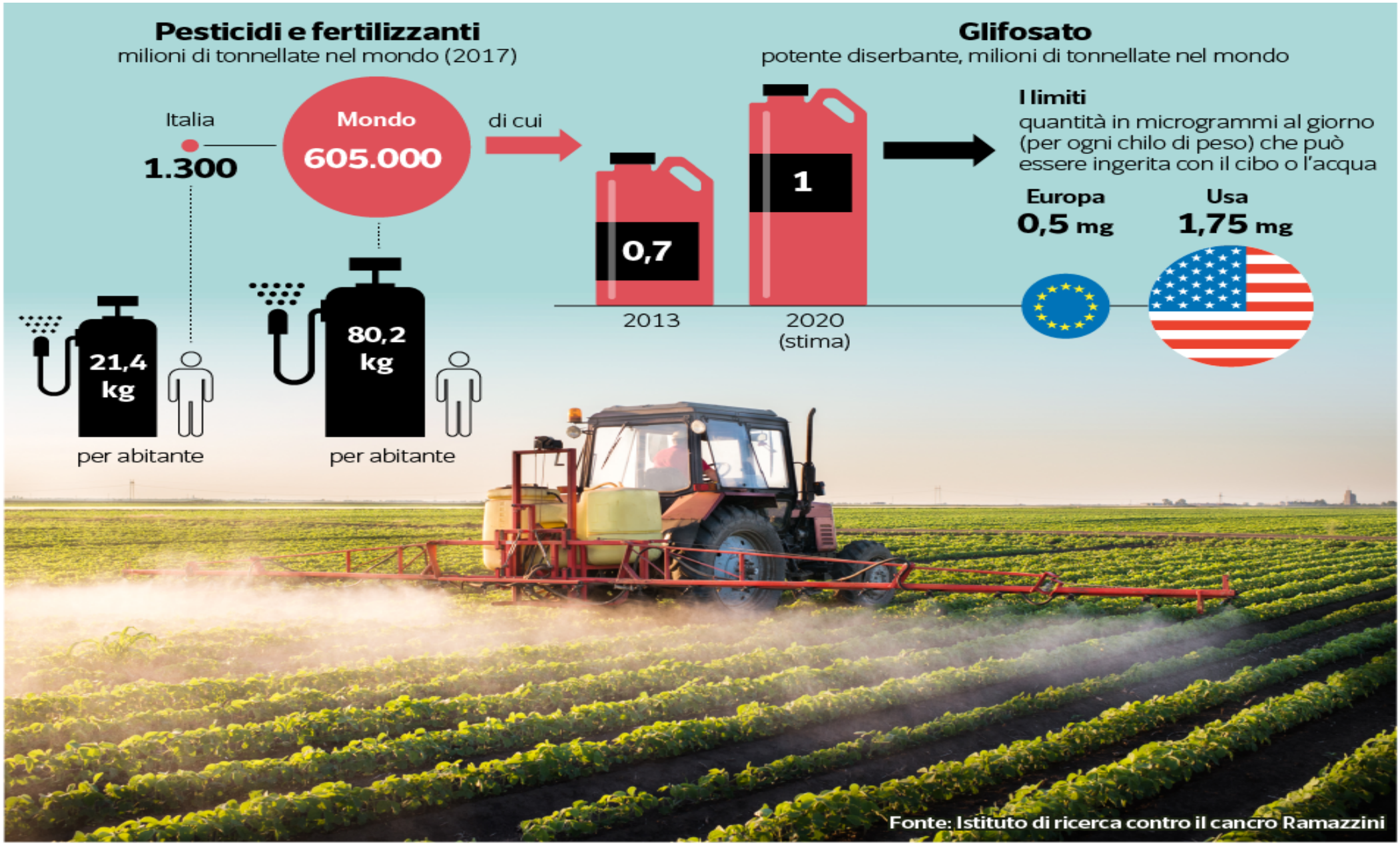
Utilizzare sempre auricolari a cavo

Non telefonare in auto e in treno

Di notte non tenere il telefono acceso sul cuscino o sul comodino

Durante la notte spegnere il wifi

Per i maschi evitare di tenerlo nella tasca dei pantaloni


Pesticidi e fertilizzanti
milioni di tonnellate nel mondo (2017)
Italia
1.300
Mondo
605.000
di cui
21,4 kg
per abitante
80,2 kg
per abitante
Glifosato
potente diserbante, milioni di tonnellate nel mondo
0,7
2013
1
2020
(stima)
I limiti
quantità in microgrammi al giorno (per ogni chilo di peso) che può essere ingerita con il cibo o l'acqua
Europa
0,5 mg
Usa
1,75 mg
Fonte: Istituto di ricerca contro il cancro Ramazzini

CORRIERE TV

International Agency
Research on Cancer

World Health
Organization

PROBABILMENTE
CANCEROGENO

PER LA RICERCA SUL CANCRO

RISULTATO UN AUMENTO DEI TUMORI AL CERVELLO

CONFERMA IL MINISTERO DELLA SALUTE FRANCESE

Global, regional, and national burden of brain and other CNS cancer, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

GBD 2016 Brain and Other CNS Cancer Collaborators*

Lancet Neurol 2019; 18: 376–93

Published Online February 20, 2019

http://dx.doi.org/10.1016/S1474-4422(18)30468-X

See Comment page 324

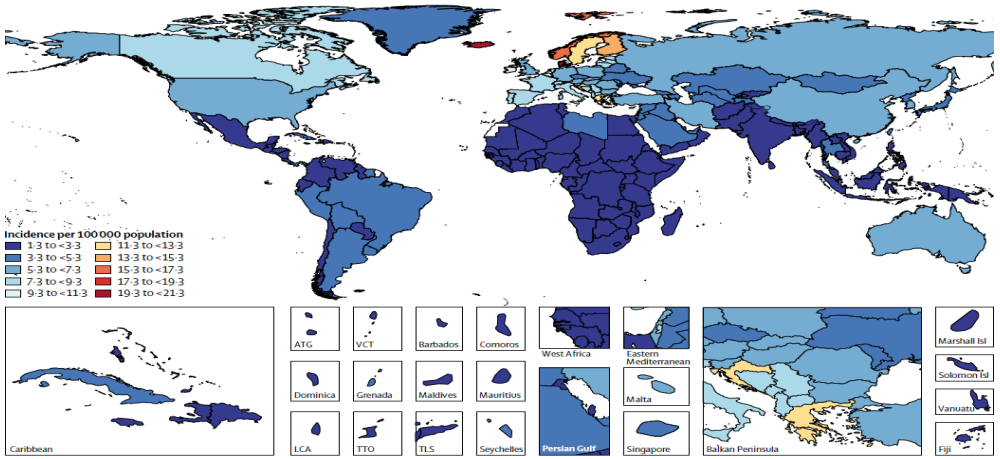
*Collaborators listed at the end of the Article

Summary

Background Brain and CNS cancers (collectively referred to as CNS cancers) are a source of mortality and morbidity for which diagnosis and treatment require extensive resource allocation and sophisticated diagnostic and therapeutic technology. Previous epidemiological studies are limited to specific geographical regions or time periods, making them difficult to compare on a global scale. In this analysis, we aimed to provide a comparable and comprehensive estimation of the global burden of brain cancer between 1990 and 2016.

Findings In 2016, there were 330 000 (95% UI 299 000 to 349 000) incident cases of CNS cancer and 227 000 (205 000 to 241 000) deaths globally, and age-standardised incidence rates of CNS cancer increased globally by 17·3% (95% UI 11·4 to 26·9) between 1990 and 2016 (2016 age-standardised incidence rate 4·63 per 100 000 person-years [4·17 to 4·90]). The highest age-standardised incidence rate was in the highest quintile of SDI (6·91 [5·71 to 7·53]). Age-standardised incidence rates increased with each SDI quintile. East Asia was the region with the most incident cases of CNS cancer 98 000 to 122 000]), followed by western Europe (49 000 [37 000 to 54 000]), and he top three countries with the highest number of incident cases were China,

Nel **2016**, ci sono stati **330.000 (da 95000 a 349000 UI da 95.000 casi) casi di carcinoma del sistema nervoso centrale** e **227000 (da 205000 a 241000) decessi a livello globale** e i tassi di incidenza standardizzati per età del carcinoma del sistema nervoso centrale sono **aumentati a livello globale del 17,3% (95% UI 11 · 4 a 26 · 9) tra 1990 e 2016** (tasso di incidenza standardizzato per età 2016 4 · 63 per 100000 persone / anno [4 · 17 a 4 · 90]).



CI STA METTENDO L'EUROPA

La spesa italiana

IN CHEMIOTERAPICI
5,6 miliardi di euro l'anno

FARMACI INNOVATIVI
614 milioni di euro
Fonte: Aifa

costano fino a **5.300** euro a ciclo
Fonte: Esmo

Esempi di terapie oncologiche tradizionali (in euro)

	1 ciclo	
polmone/ mesotelioma	**2.071,81**	(media 4 cicli)
pancreas	**1.649,85**	(media 4 cicli)
mammella	**1.115,29**	(media 6 cicli)
gastroenterico	**107,12**	(media 6 cicli)

Fonte: elaborazione Dataroom

RICERCA SUL CANCRO
210 milioni l'anno

Fonte: Alleanza contro il Cancro

21 milioni
su cosa lo provoca

Gli studi a confronto su esposizione alle radiofrequenze

Istituto di ricerca	Anno	Cavie esposte	Per quanto tempo	Frequenza di esposizione (MHz)	Esposizione totale: ore al giorno	Esposizione totale: giorni alla settimana	Risultato
Chou (e al.)	1992	400	25 mesi	**2.450**	**21,5**	**7**	**Tumori primari linfoma maligno carcinoma tiroideo**
La Regina (e al.)	2003	160	24 mesi	**835,62 e 847,74**	**4**	**5**	**Negativo**
Anderson (e al.)	2004	180	24 mesi	**1.600**	**2**	**5**	**Negativo**
Smith (e al.)	2007	130	24 mesi	**900 e 1.800**	**2**	**5**	**Negativo**
Wyde (e al.) Ntp	2016	210	Da prima della nascita per 24 mesi	**900**	**9**	**7**	**Glioma cerebrale maschile e Schwannoma del cuore**
Falcioni (e al.) Istituto Ramazzini	2018	1.200	Da prima della nascita fino alla morte	**1.800**	**19**	**7**	**Schwannoma del cuore maschile e Glioma cerebrale femminile**

Fonte: Istituto di ricerca contro il cancro Ramazzini

Mutation Research 704 (2010) 115–122

Contents lists available at ScienceDirect

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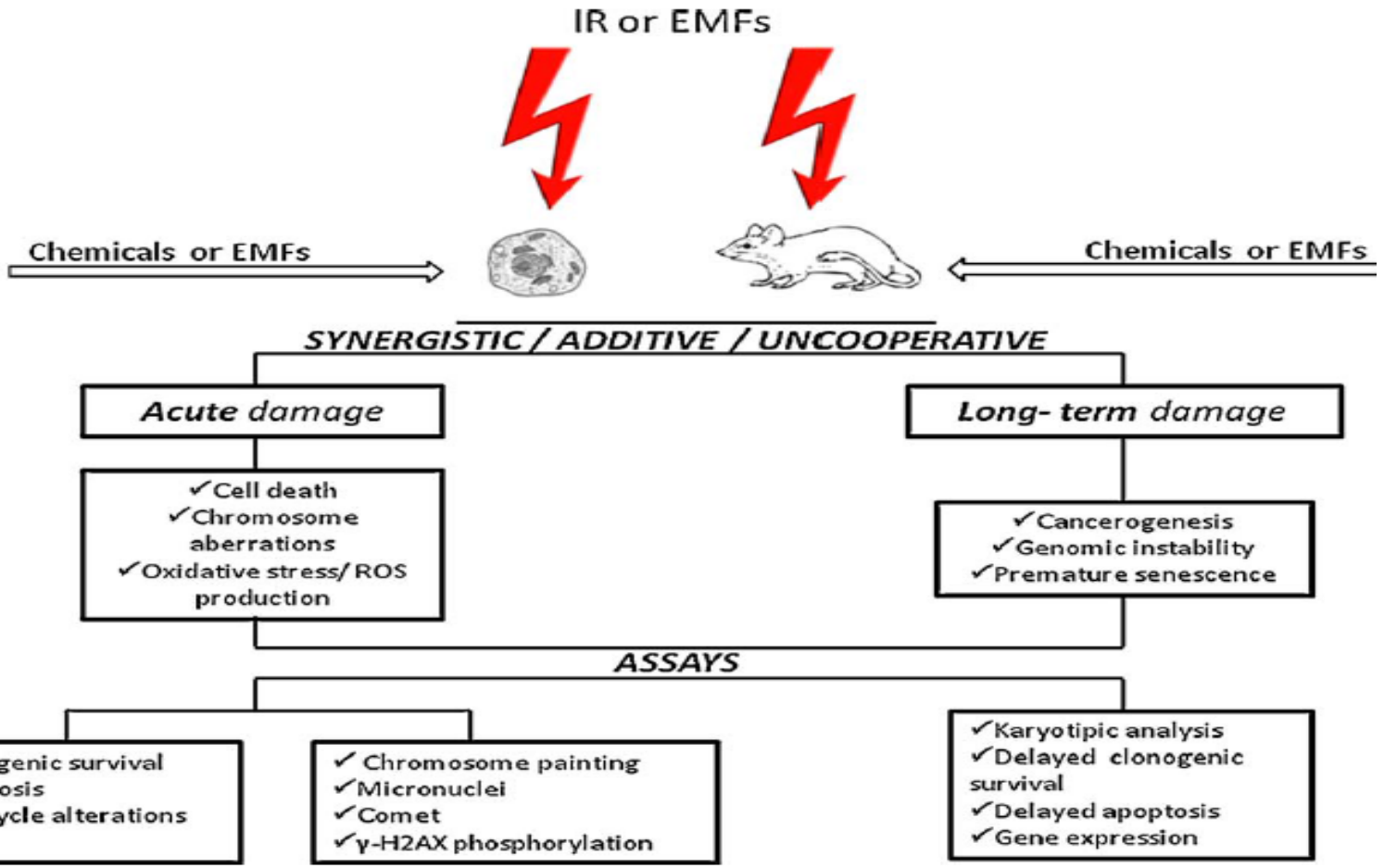
Review

Cooperative biological effects between ionizing radiation and other physical and chemical agents

Lorenzo Manti *, Annalisa D'Arco

Exposure to ionizing radiation (IR), at environmentally and therapeutically relevant doses or as a result of diagnostics or accidents, causes cyto- and genotoxic damage. However, exposure to IR alone is a rare event as it occurs in spatial and temporal combination with several physico-chemical agents. Some of these are of known noxiousness, as is the case with chemical compounds at high dose, hence additive/synergistic effects can be expected or have been demonstrated. Conversely, the cellular toxicity of other agents, such as non-ionizing electromagnetic fields (EMFs), is only presumed and their short- and long-term cooperation on IR-induced damage remains undetermined. In this review, we shall examine evidence in support of the interplay between spatially and/or temporally related environmentally relevant stressors. *In vitro* or animal-based studies as well as epidemiological surveys have generally

.. recent **data on the interaction between ELF EMFs and chemicals show delayed chromosomal instability arising in human fibroblasts** [67]…Suggestions of **long-lasting inhibition of DNA repair by UMTS/GSM signals** were made based on the observed persistence of the **reduction in 53BP1/γ-H2AX colocalized foci** [97].
Hence, **RF may epigenetically modulate genomic instability inducible by chronical chemical exposure and/or IR ...** Therefore, it is of interest **to investigate the long-term cooperative effects arising from combined exposure scenarios (Fig. 1).**



Very little data are currently available on the **cumulative effects of exposure to multiple hazardous agents that have either similar or different mechanisms of action on DNA**.. In addition to known mutagens, **presumptive DNA-damaging agents, such as EMFs fields, ought to be also considered since they may influence cellular responses to IR or chemicals, for instance by sublethal stress generation**

PLoS One. 2017 May 4;12(5):e0175136. doi: 10.1371/journal.pone.0175136

Mobile phone use and glioma risk: A systematic review and meta-analysis

Ming Yang[1☯], WenWen Guo[2☯], ChunSheng Yang[3☯], JianQin Tang[4], Qian Huang[2], ShouXin Feng[1]*, AiJun Jiang[1], XiFeng Xu[1], Guan Jiang[4]*

Results

There was a significant positive association between long-term mobile phone use (minimum, 10 years) and glioma (OR = 1.44, 95% CI = 1.08–1.91). And there was a significant positive association between long-term ipsilateral mobile phone use and the risk of glioma (OR = 1.46, 95% CI = 1.12–1.92). Long-term mobile phone use was associated with 2.22 times greater odds of low-grade glioma occurrence (OR = 2.22, 95% CI = 1.69–2.92). Mobile phone use of any duration was not associated with the odds of high-grade glioma (OR = 0.81, 95% CI = 0.72–0.92). Contralateral mobile phone use was not associated with glioma regardless of the duration of use. Similarly, this association was not observed when the analysis was limited to high-grade glioma.

C'è **un'associazione significativa tra uso a lungo termine di telefoni cellulari (minimo, 10 anni) e glioma** (OR = 1,44, IC 95% = 1,08-1,91). .. E una significativa associazione positiva tra **uso a lungo termine di telefoni cellulari e rischio di glioma omolaterale** (OR = 1,46, IC 95% = 1,12-1,92)

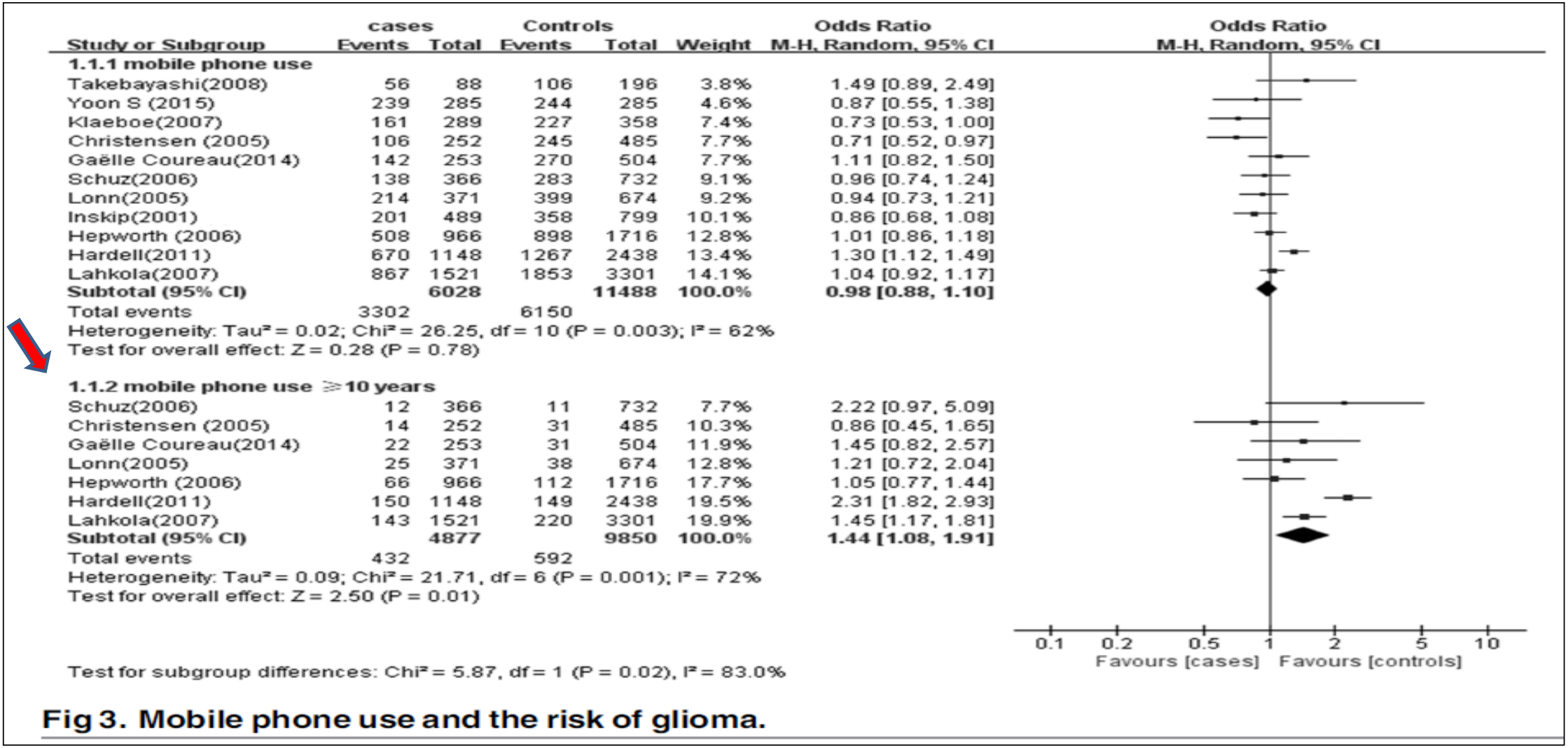
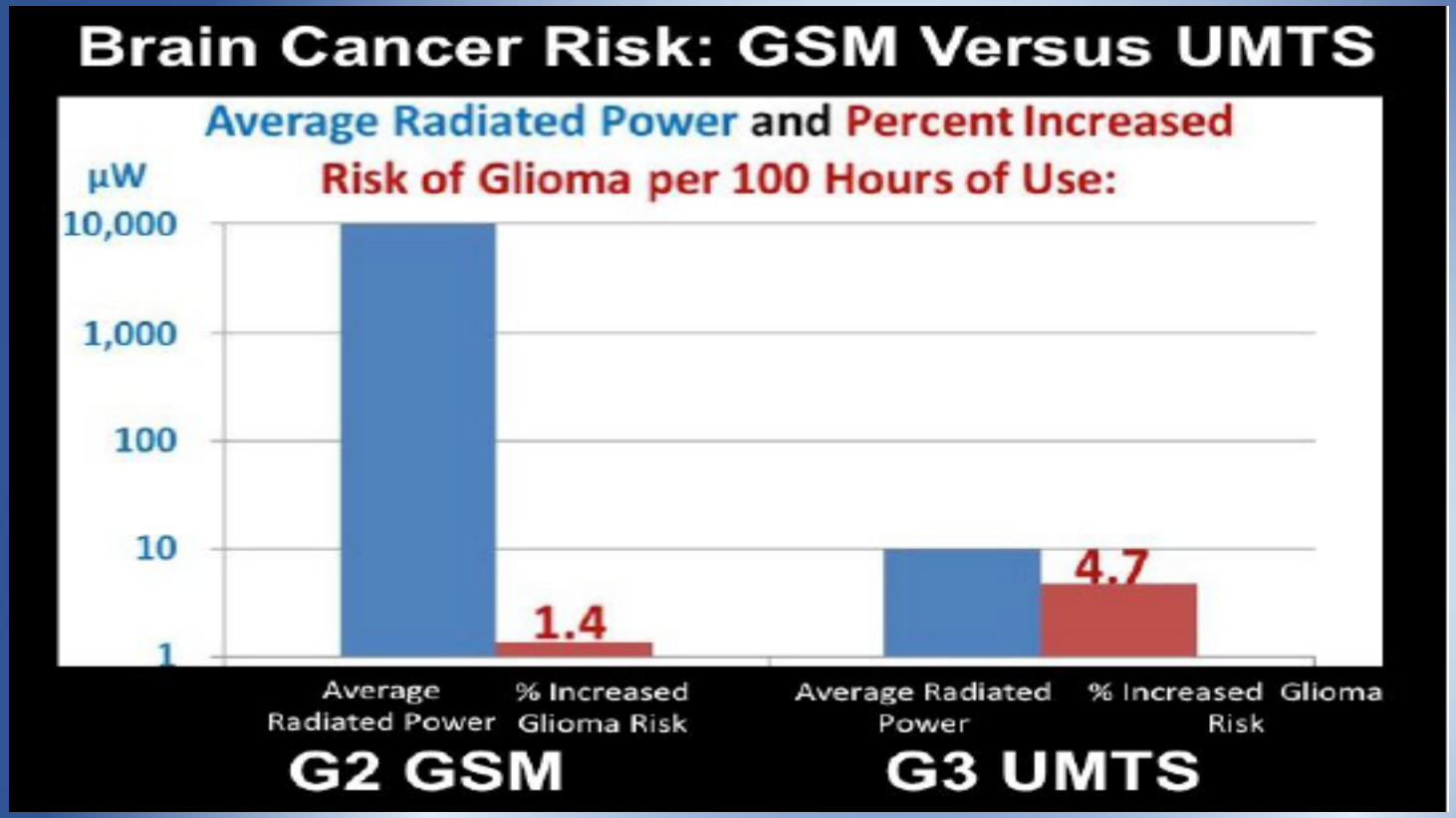
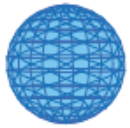


Fig 3. Mobile phone use and the risk of glioma.



As a recent example, consider the recent research that compares 2G (GSM technology) to 3G (UMTS-talk, text, and data- Smartphone technology). People usually assume, the more power you absorb, the higher the risk. However, when scientists reviewed the first ever paper that looks at brain cancer risk by type of phone used- 2 or 3 G- they came to a stunning conclusion. The *lower* power 3G UMTS phones had a higher glioma (a type of brain cancer) risk than the *higher* power 2G GSM phones. Although 3G technology has up to 1000 less power, this technology shows a more than three times for glioma in comparison to 2G. These differences speak to the complexity of understanding wireless communication exposures and how various signal characteristics, such as modulation and waveform

Levis *et al. Environmental Health* 2011, **10**:59
http://www.ehjournal.net/content/10/1/59



ENVIRONMENTAL HEALTH

RESEARCH Open Access

Mobile phones and head tumours. The discrepancies in cause-effect relationships in the epidemiological studies - how do they arise?

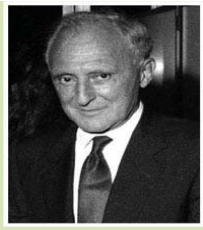
Angelo G Levis[1], Nadia Minicuci[2], Paolo Ricci[3], Valerio Gennaro[4] and Spiridione Garbisa[1*]

Results: Blind protocols, free from errors, bias, and financial conditioning factors, give positive results that reveal a cause-effect relationship between long-term mobile phone use or latency and statistically significant increase of ipsilateral head tumour risk, with biological plausibility. Non-blind protocols, which instead are affected by errors, bias, and financial conditioning factors, give negative results with systematic underestimate of such risk. However, also in these studies a statistically significant increase in risk of ipsilateral head tumours is quite common after more than 10 years of mobile phone use or latency. The meta-analyses, our included, examining only data on ipsilateral tumours in subjects using mobile phones since or for at least 10 years, show large and statistically significant increases in risk of ipsilateral brain gliomas and acoustic neuromas.

Cellphone Biological Studies							
		Effect Found		No Effect Found			
		Studies	% All Studies	Studies	% All Studies	Studies	% All Studies
Industry Funded	No.	27	8.3%	69	21.2%	96	29.4%
	%	28.1%		71.9%			
Independently Funded	No.	[illegible]	47.5%	[illegible]	23.5%	230	70.6%
	%	67.0%		33.0%			
Totals		[illegible]	55.5%	[illegible]	44.5%	326	100.0%

Chi^2 =39.8 ($p=2.3x10^{-9}$) 11 July 2006 [1]

Table 1: Industry-Funded and Independently-Funded Cellphone Biological Studies



1: Ann N Y Acad Sci. 2002 Dec;982:190-7.

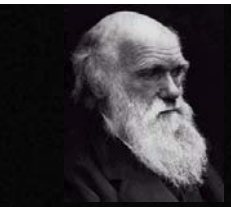
Three decades after the first formulations of a theory about the foetal origin of some cancers, in a **world characterized by an ubiquitous distribution of thousands of potentially pro-carcinogenic molecules in food chains and even in the cord blood and placentas..** it is useful to recall **Tomatis's great lesson**: in order to reverse the trend of continuous increase in tumours, **primary prevention is necessary and urgent**.

Primary prevention protects public health.

Tomatis L.

Cave 25/r, 34011 Aurisina (Trieste), Italy. ltomatis@hotmail.com

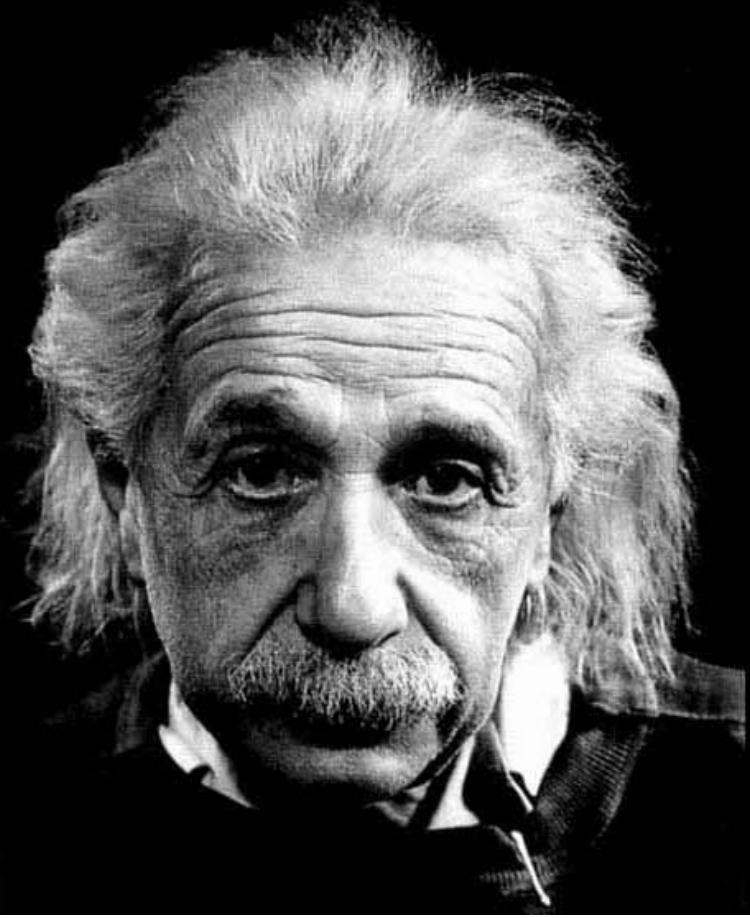
It is widely accepted that epidemiological data provide the only reliable evidence of a carcinogenic effect in humans, but epidemiology is unable to provide early warning of a cancer risk. The experimental approach to carcinogenicity can ascertain and predict potential cancer risks to humans in time for primary prevention to be successful. Unfortunately, only in rare instances were experimental data considered sufficiently convincing per se to stimulate the adoption of preventive measures. The experimental testing of environmental agents is the second line of defense against potential human carcinogens. The first line is the testing of synthesized agents, be these pesticides, medical drugs, or industrial chemical/physical agents, at the time of their development. We do not know, however, how many substances have been prevented from entering the environment because most tests are carried out by commercial or private laboratories and results are rarely released. A better understanding of the mechanisms underlying the sequence of events of the carcinogenesis process will eventually lead to a more accurate characterization and quantification of risks. However, the ways that mechanistic data have been used lately for evaluating evidence of carcinogenicity have not necessarily meant that the evaluations were more closely oriented toward public health. A tendency has surfaced to dismiss the relevance of long-term carcinogenicity studies. In the absence of absolute certainty, rarely if ever reached in biology, it is essential to adopt an attitude of responsible caution, in line with the principles of primary prevention, the only one that may prevent unlimited experimentation on the entire human species.


"Everything should be made as simple as possible, but not simpler."

Albert Einstein

God is **subtle** but not malicious



God does **not** play dice

È la celebre affermazione che suggella l'acceso dibattito tra Einstein e i sostenitori di una certa interpretazione della fisica quantistica…

I believe in Spinoza's God who reveals himself in the orderly harmony of what exists

"We ***can't solve*** problems by using the ***same kind of thinking*** we used when we ***created*** them"

"A clever man ***solves*** a problem, a wise man ***avoids*** it"