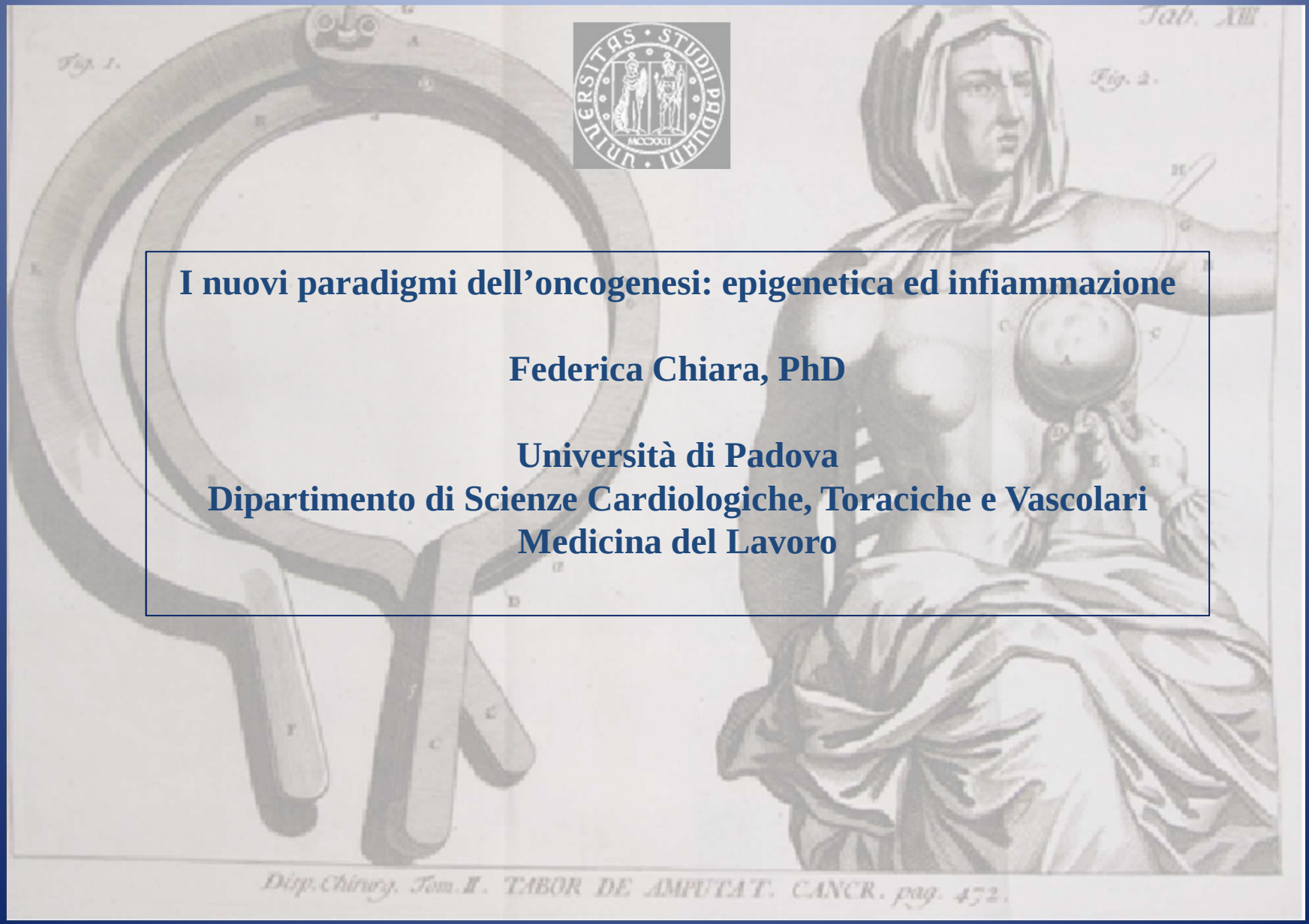


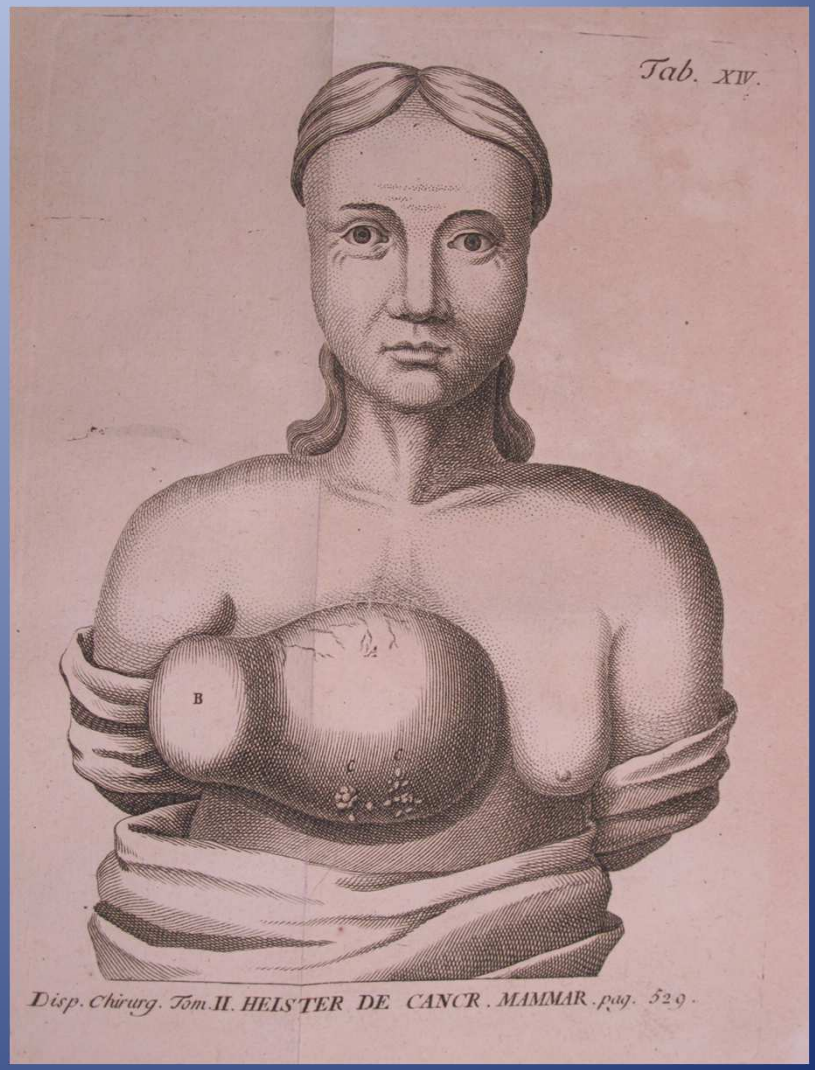
I nuovi paradigmi dell'oncogenesi: epigenetica ed infiammazione

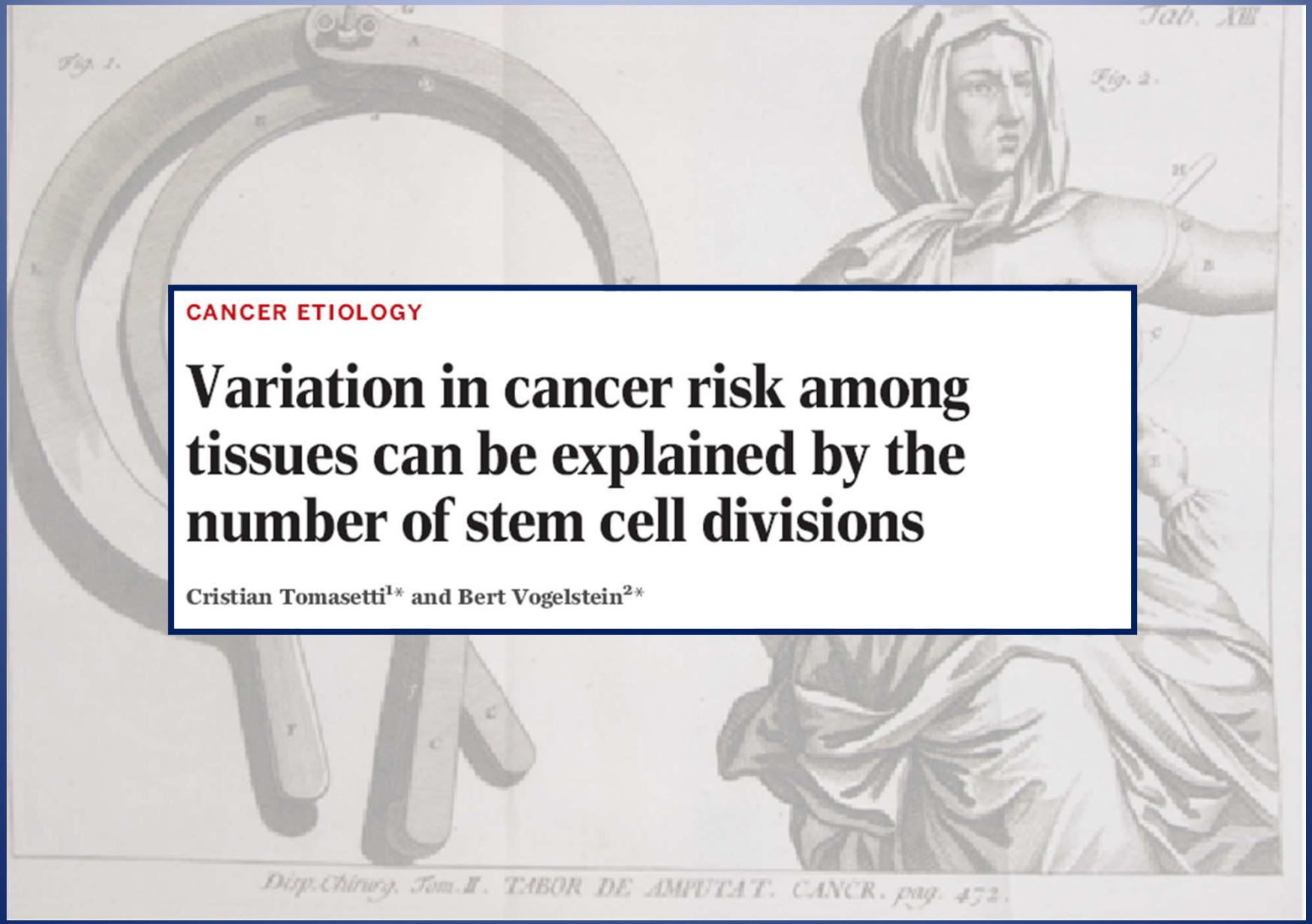
Federica Chiara, PhD

Università di Padova
Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari
Medicina del Lavoro

“il medico competente programma ed effettua la sorveglianza sanitaria [...] attraverso protocolli sanitari definiti in funzione dei rischi specifici e tenendo in considerazione gli indirizzi scientifici più avanzati“.

D. Lgs. 81/2008, all'art. 25, comma b





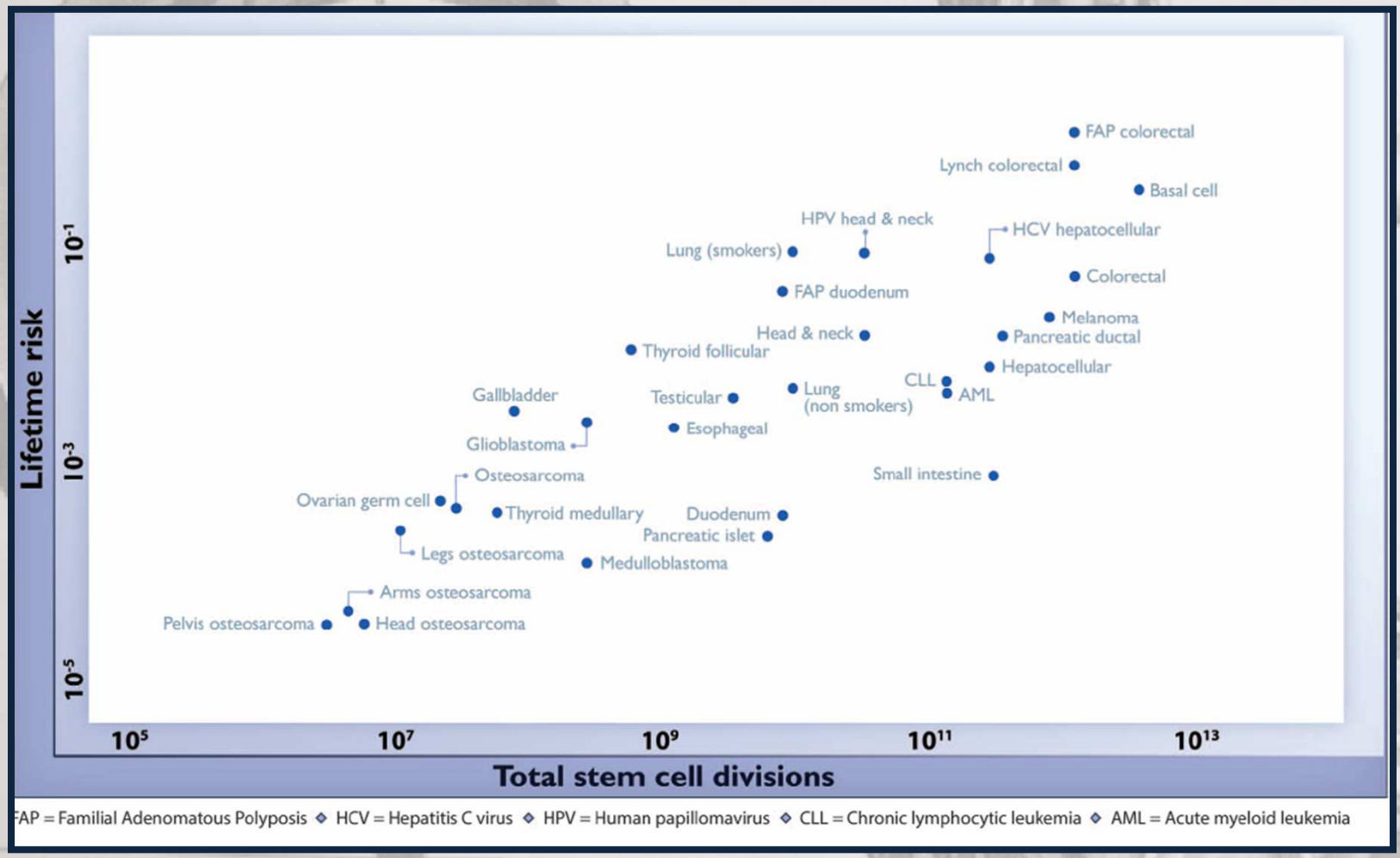
CANCER ETIOLOGY

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

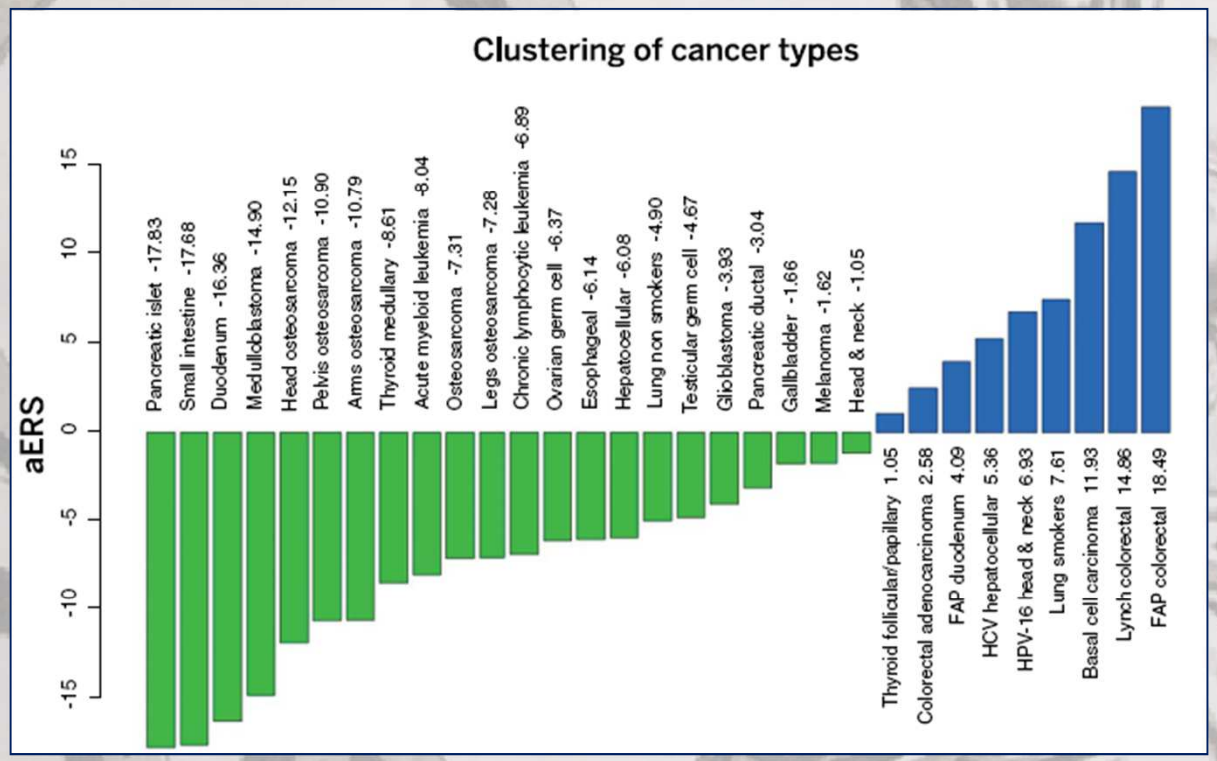
Cristian Tomasetti[1]* and Bert Vogelstein[2]*

Science 2 JANUARY 2015 • VOL 347 ISSUE 6217

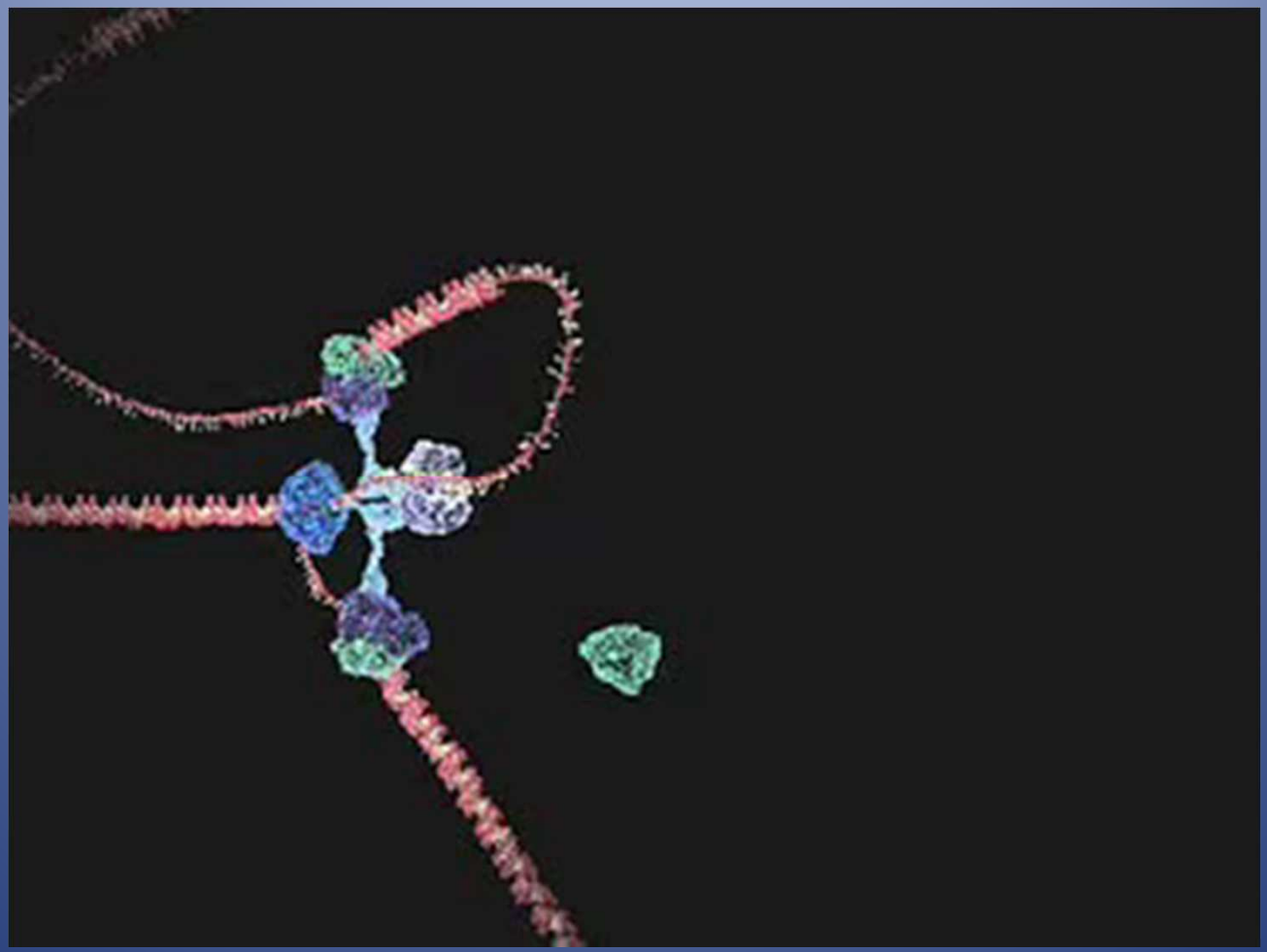
Il numeri di cicli cellulari delle staminali correla con l'incidenza dei tumori

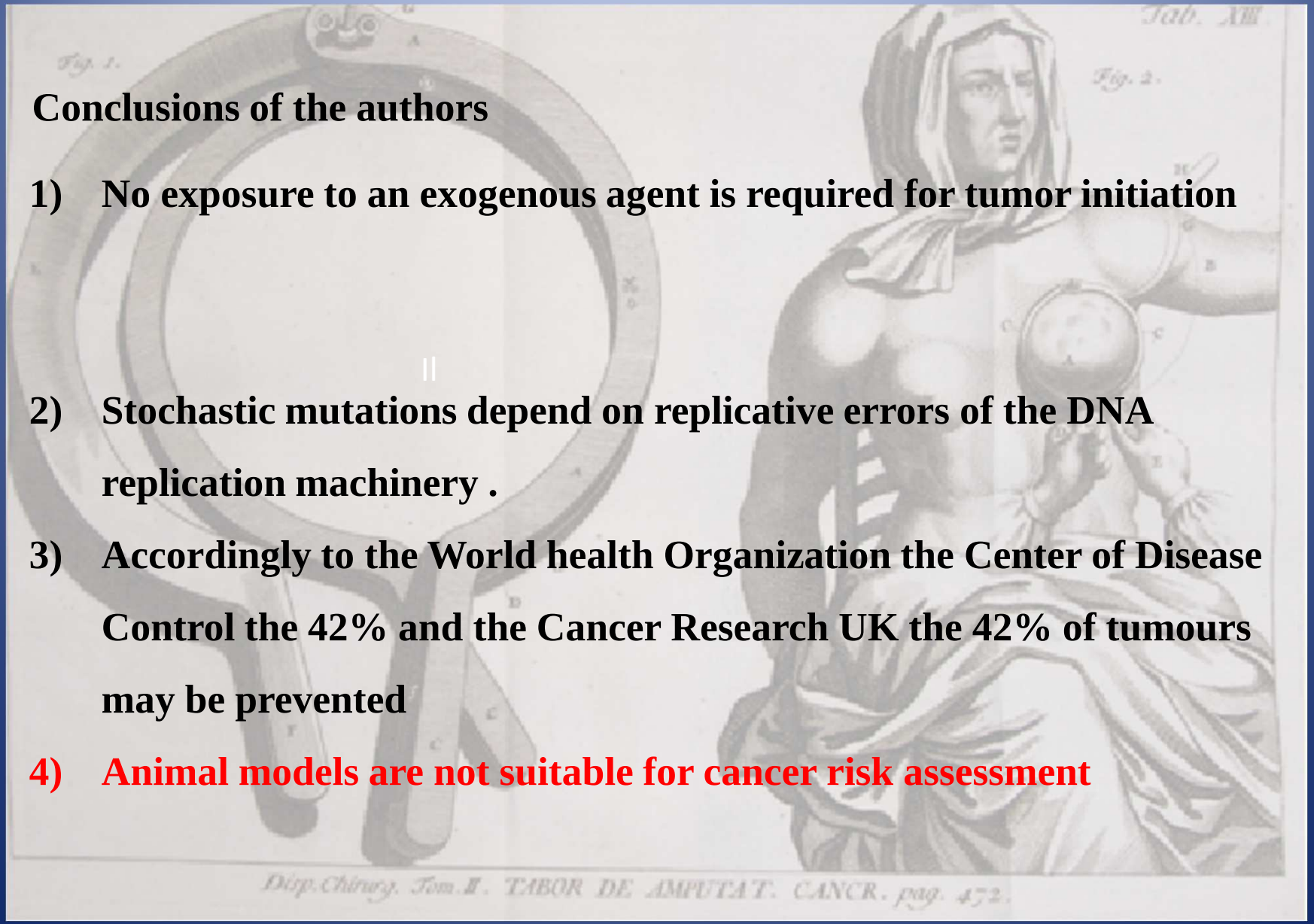


Il numero di cicli cellulari delle staminali correla con l'incidenza dei tumori



Science 2 JANUARY 2015 • VOL 347 ISSUE 6217





Conclusions of the authors

1) **No exposure to an exogenous agent is required for tumor initiation**

2) **Stochastic mutations depend on replicative errors of the DNA replication machinery .**

3) **Accordingly to the World health Organization the Center of Disease Control the 42% and the Cancer Research UK the 42% of tumours may be prevented**

4) **Animal models are not suitable for cancer risk assessment**

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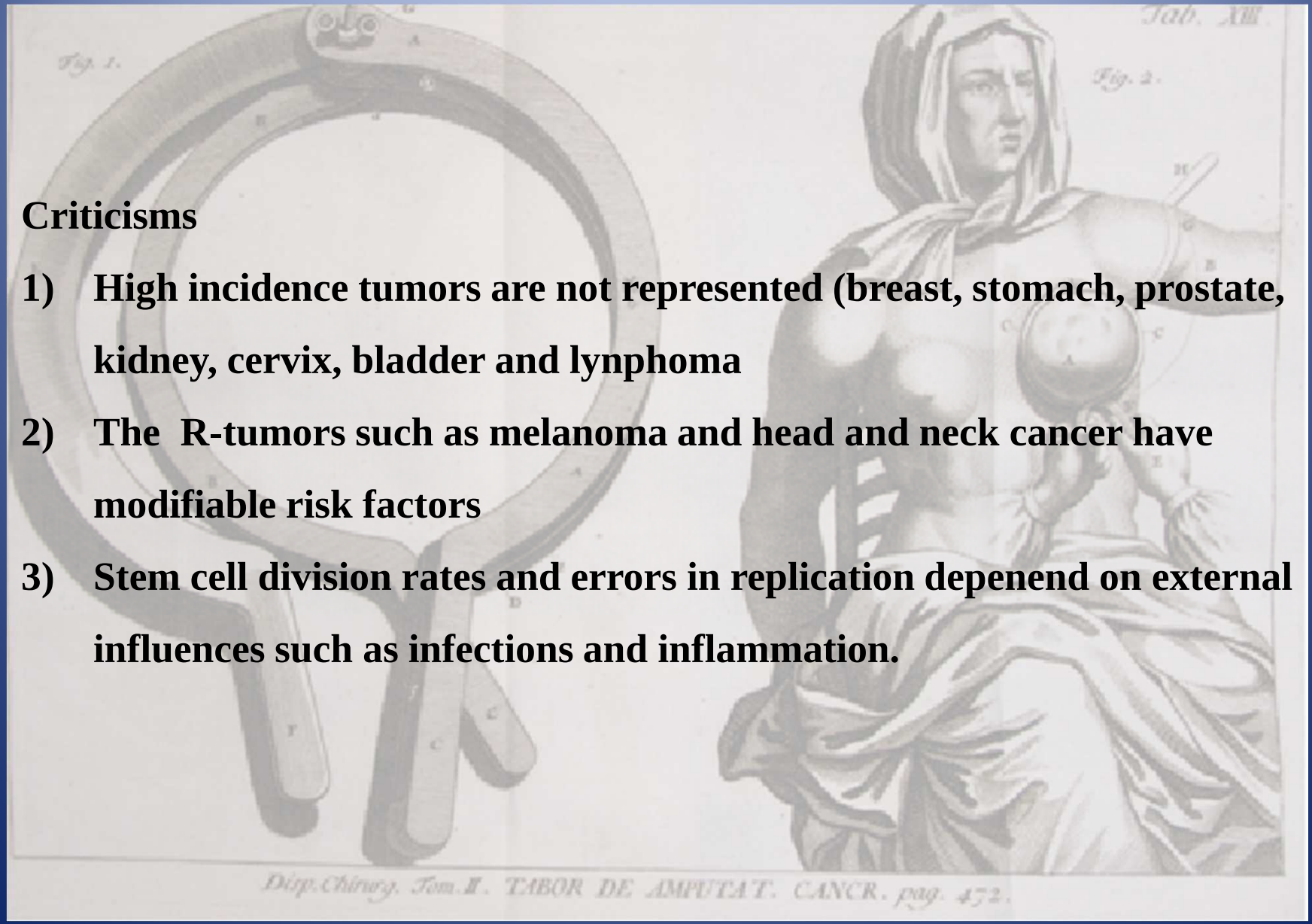


Criticisms

1) **High incidence tumors are not represented (breast, stomach, prostate, kidney, cervix, bladder and lynphoma**
2) **The R-tumors such as melanoma and head and neck cancer have modifiable risk factors**
3) **Stem cell division rates and errors in replication depenend on external influences such as infections and inflammation.**

LINEAR MODEL (CARCINOGENS)

CR (cancer risk) = dose x SF

SF is a slope factor defined for each substance

Italian low (D.Lgs 152/2006)

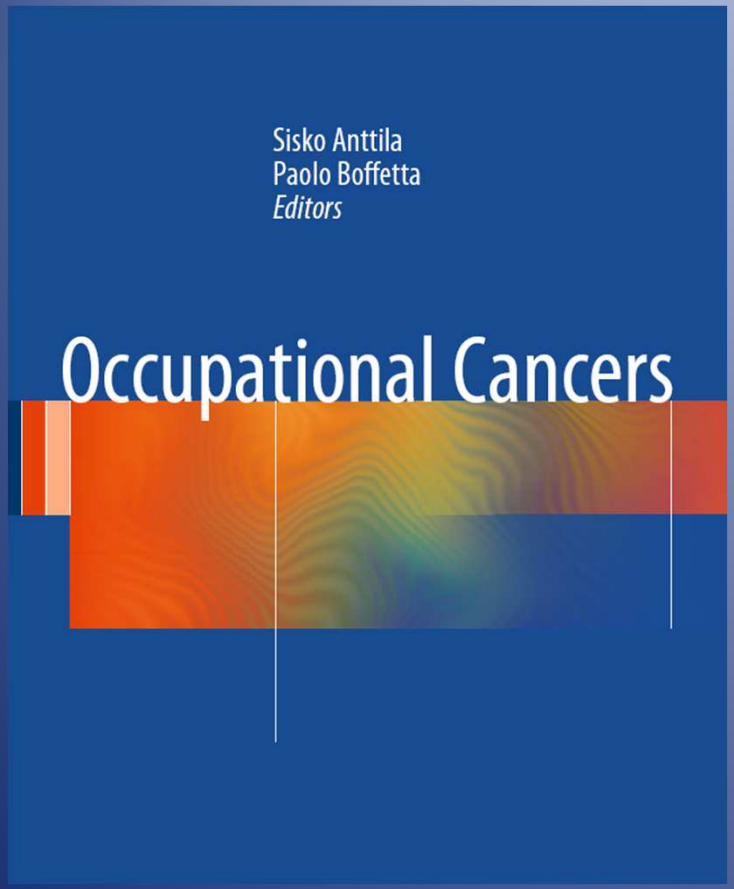
HI < 1 no risk

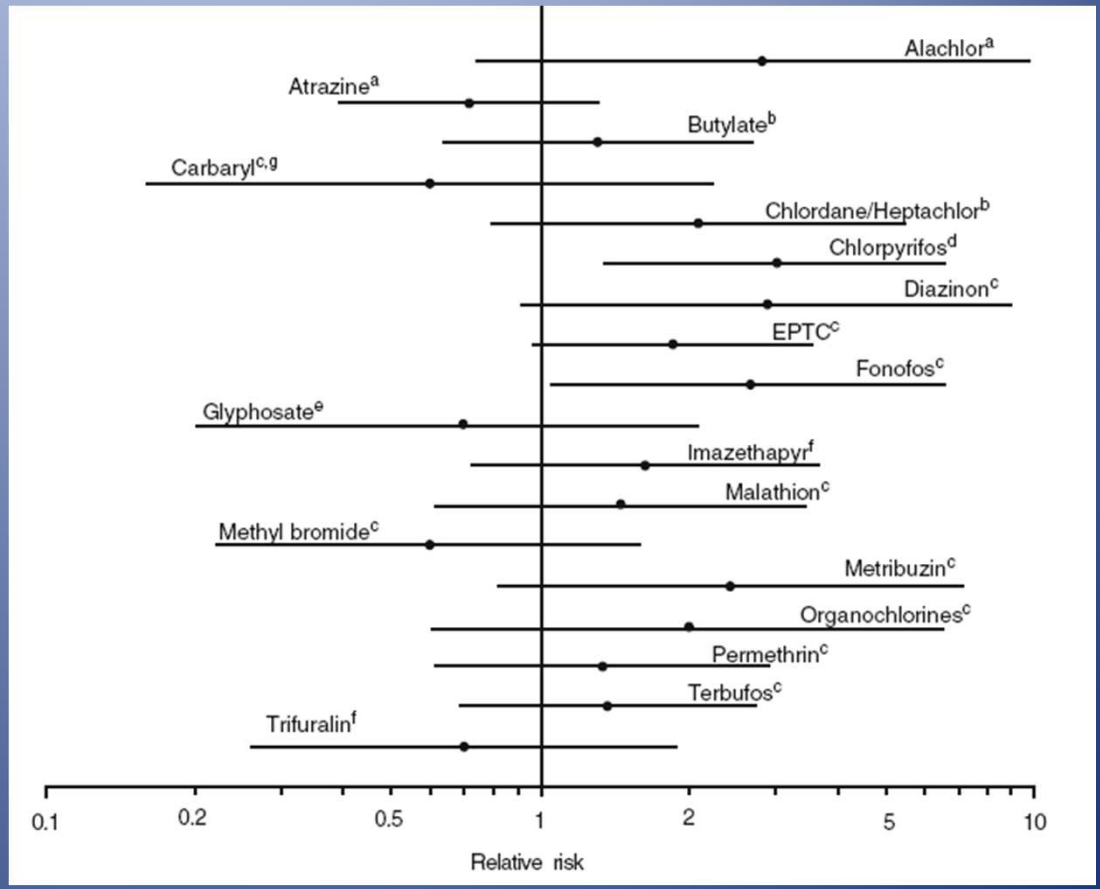
R < 10^{-5} Risk threshold

Assunzione giornaliera accettabile (ADI) o Dose di riferimento di rischio (RfD)

$$RfD = \frac{NOAEL}{UF_{interspecies} X UF_{intraspecies} X MF}$$

Fattori di Incertezza: H, A, S, I, D


Sisko Anttila
Paolo Boffetta
Editors
Occupational Cancers


Alachlor[a]
Atrazine[a]
Butylate[b]
Carbaryl[c,g]
Chlordane/Heptachlor[b]
Chlorpyrifos[d]
Diazinon[c]
EPTC[c]
Fonofos[c]
Glyphosate[e]
Imazethapyr[f]
Malathion[c]
Methyl bromide[c]
Metribuzin[c]
Organochlorines[c]
Permethrin[c]
Terbufos[c]
Trifuralin[f]
0.1
0.2
0.5
1
2
5
10
Relative risk

Field cancerization: the lung example

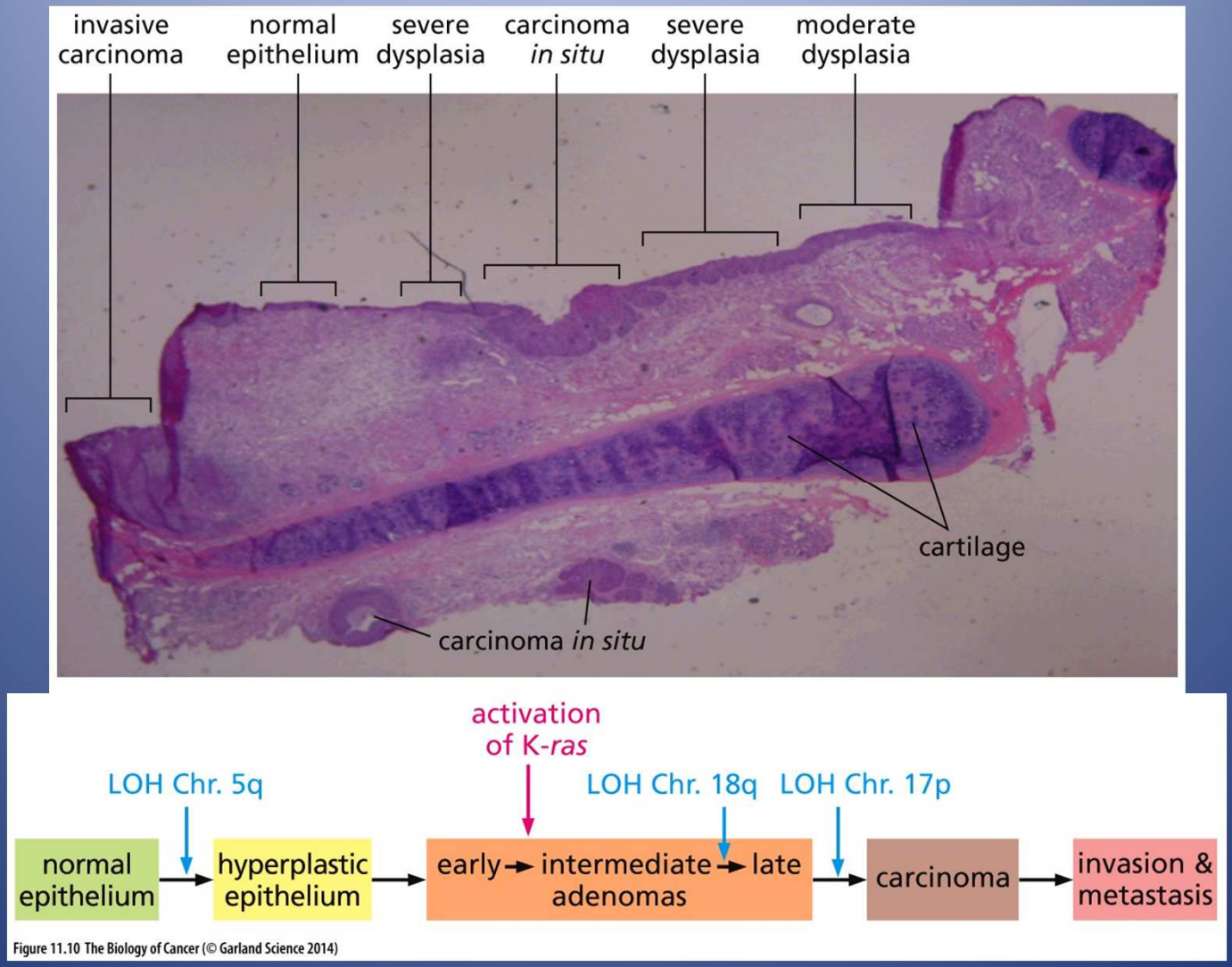
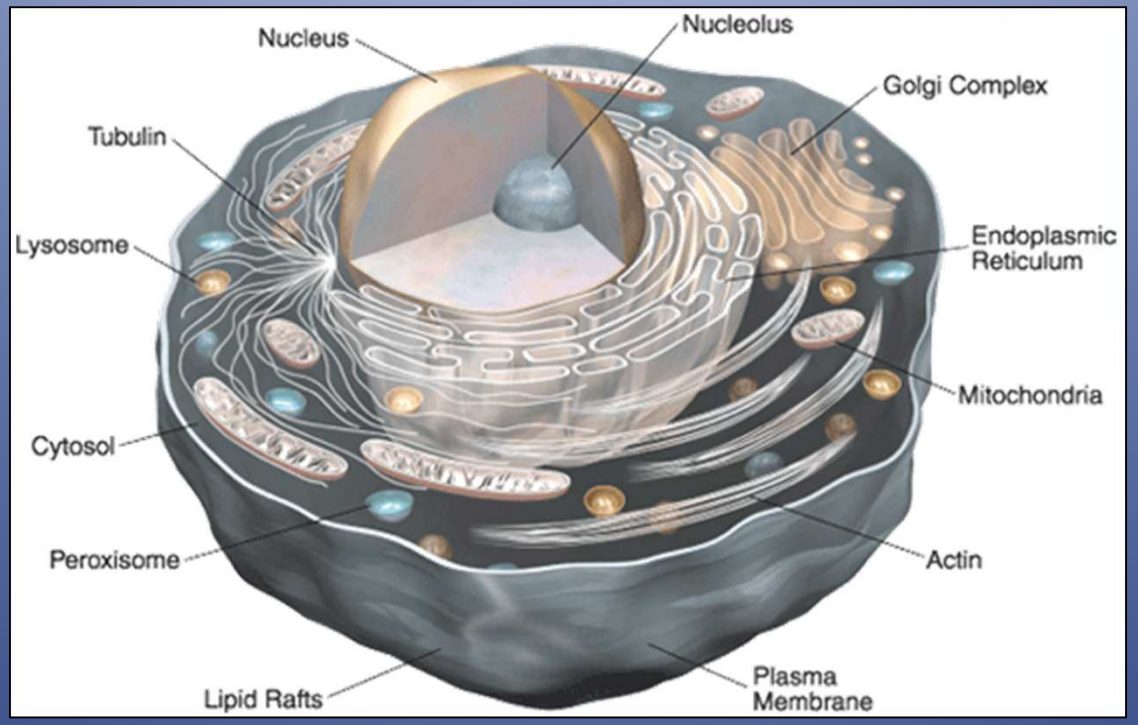


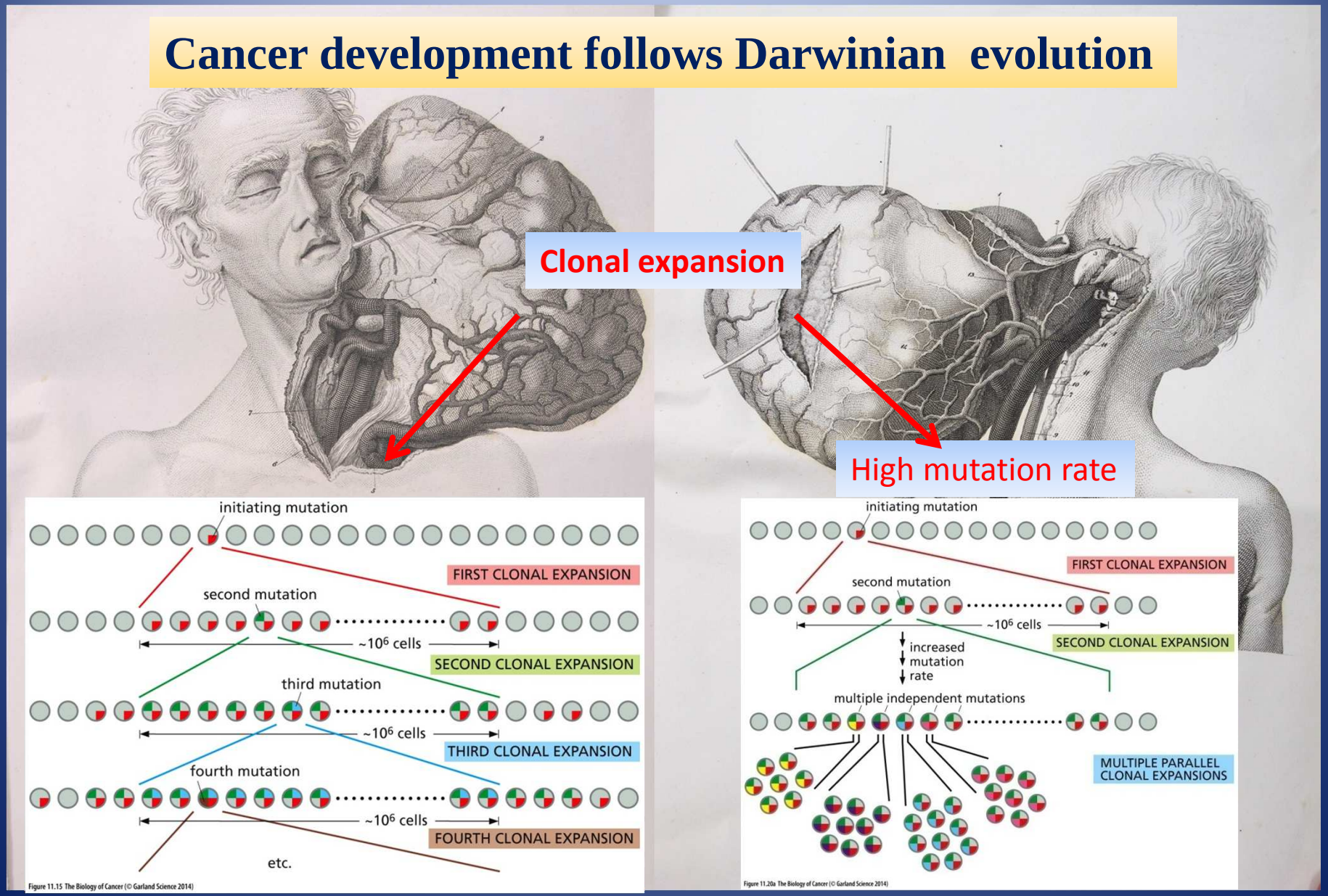
Figure 11.10 The Biology of Cancer (© Garland Science 2014)

Cancer Res. 63: 1727-1730. 2003

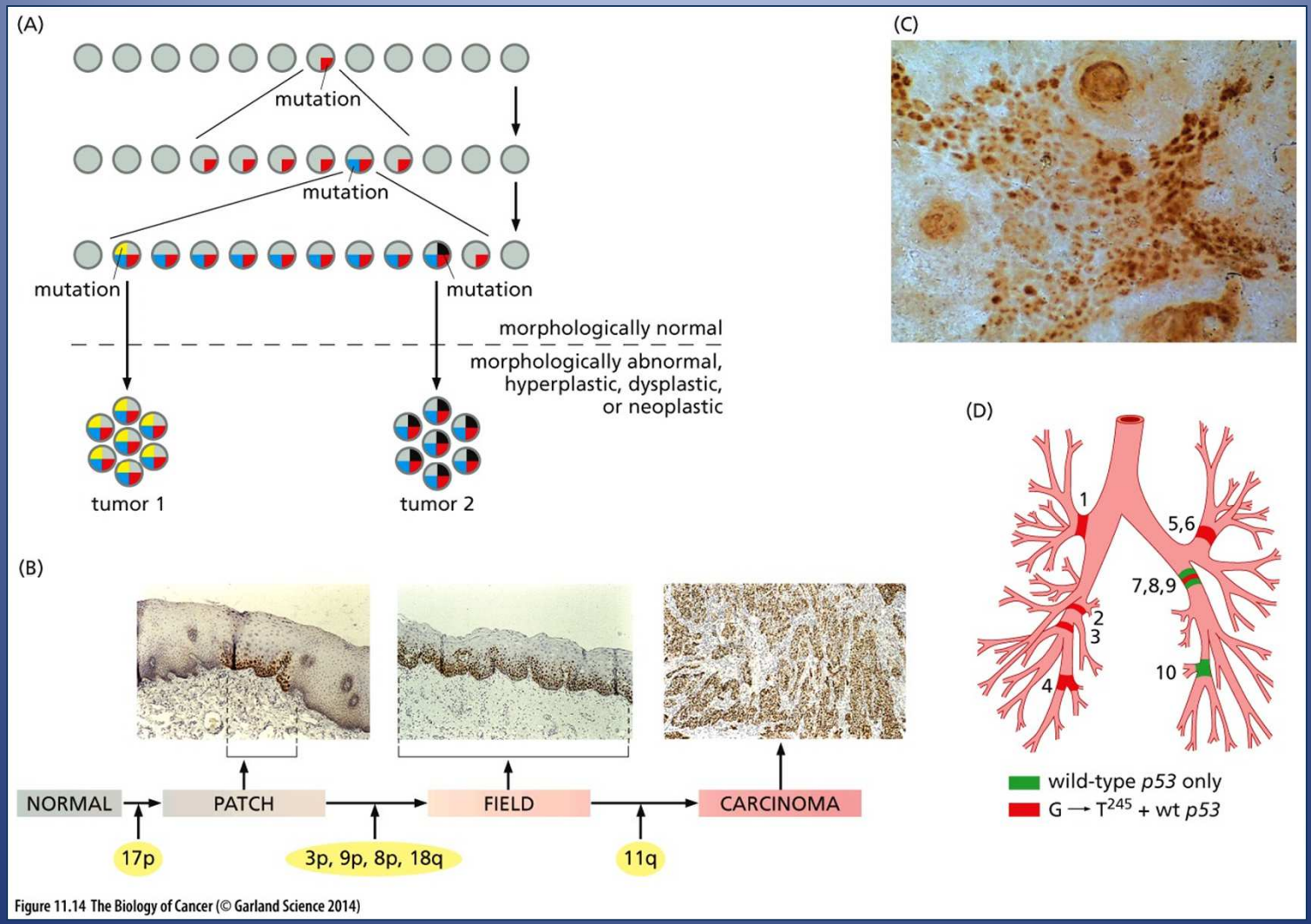
A step back inside the cell…



Cancer development follows Darwinian evolution

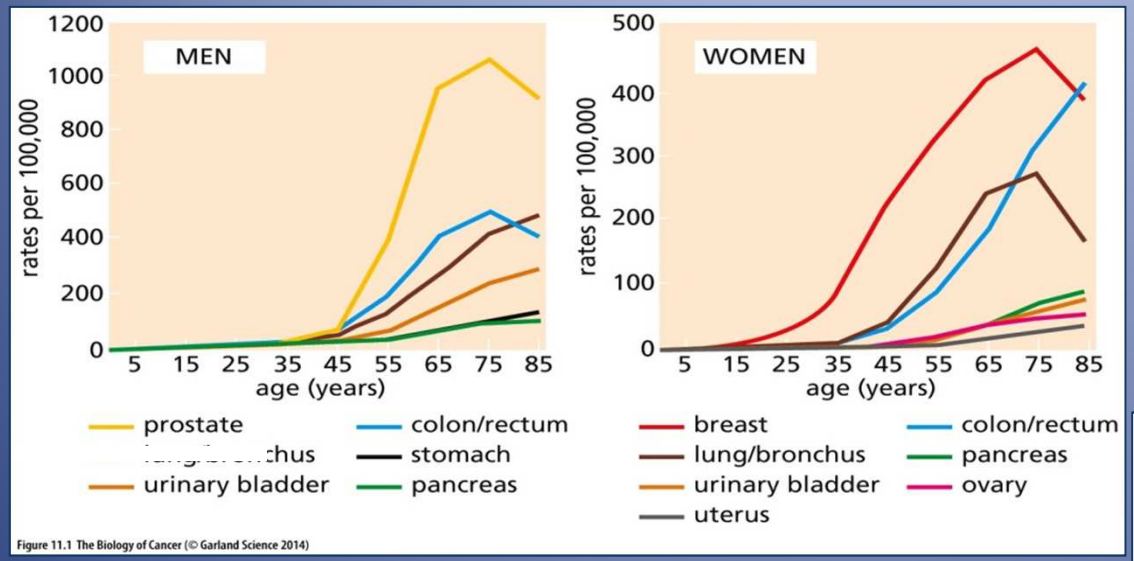


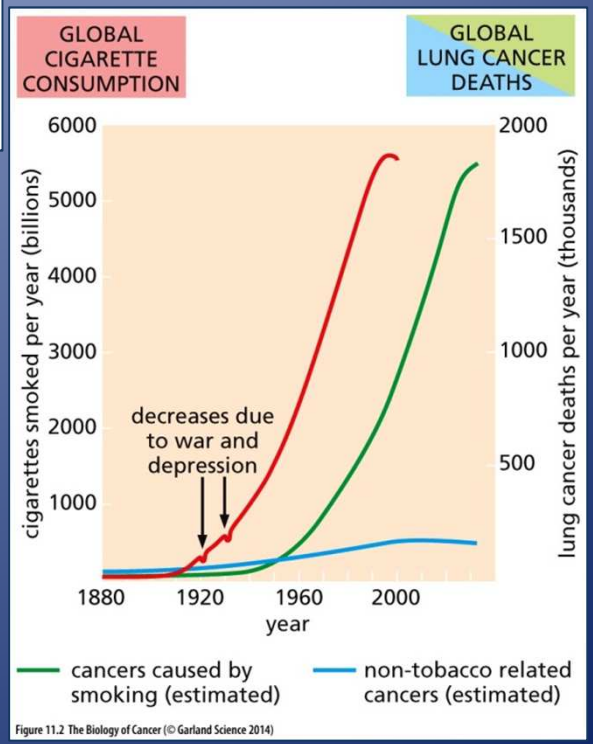
Field cancerization



Cancer Res. 63: 1727-1730. 2003

Human Cancers develop over many decades of time: the age factor





From W.K. Wong SEER Cancer Statistic Review
R.N. Proctor, Nat.Rev. Cancer 1:82-86, 2001

Exceptions

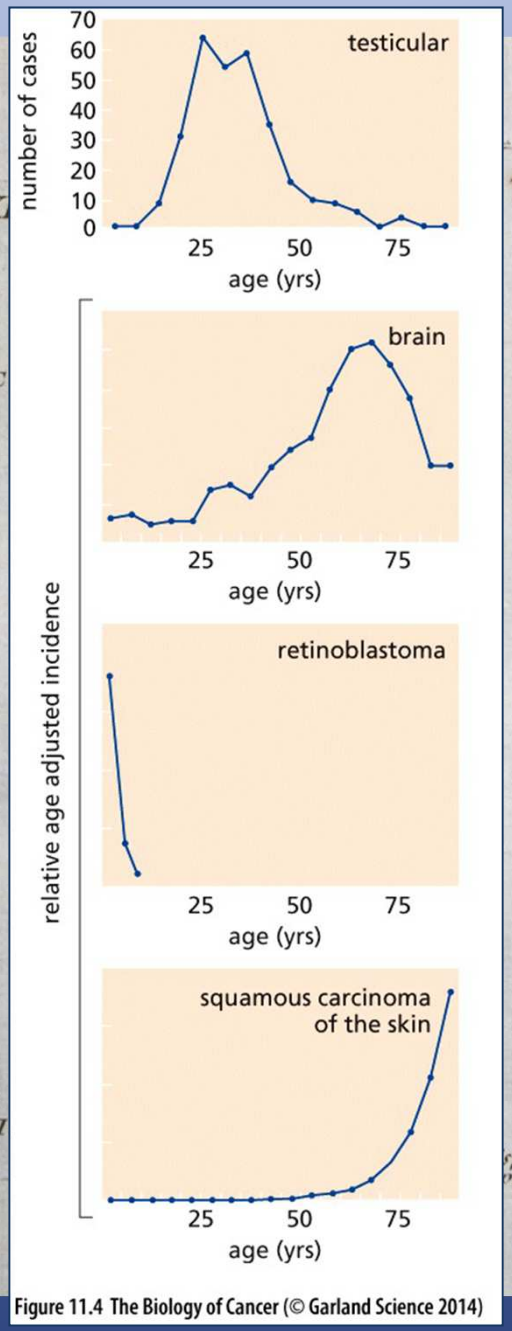
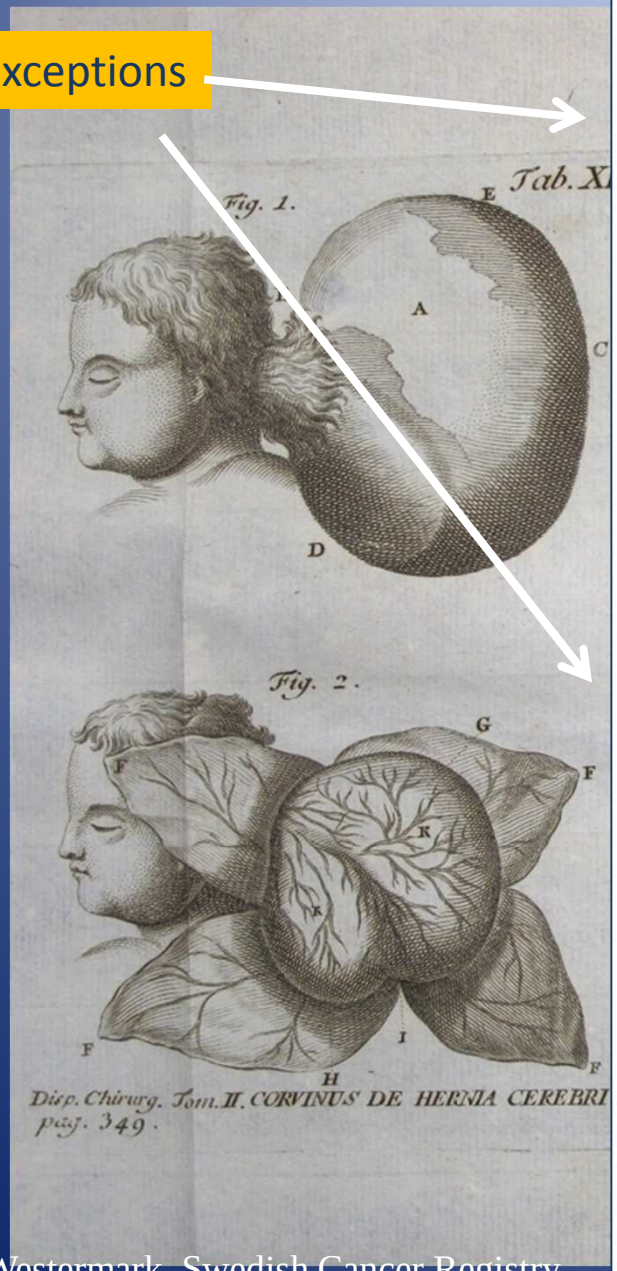
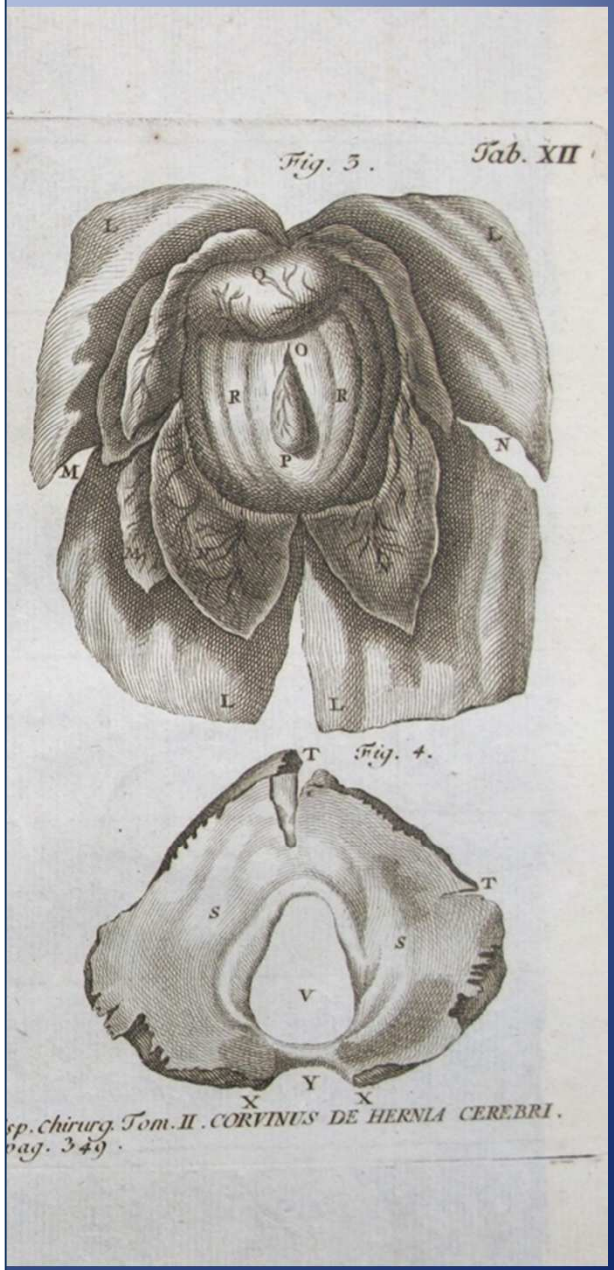


Figure 11.4 The Biology of Cancer (© Garland Science 2014)





B. Westermark, Swedish Cancer Registry
J.Li et al. Pediatrics 121:e1470-e1477

The Multi-Step tumorigenesis

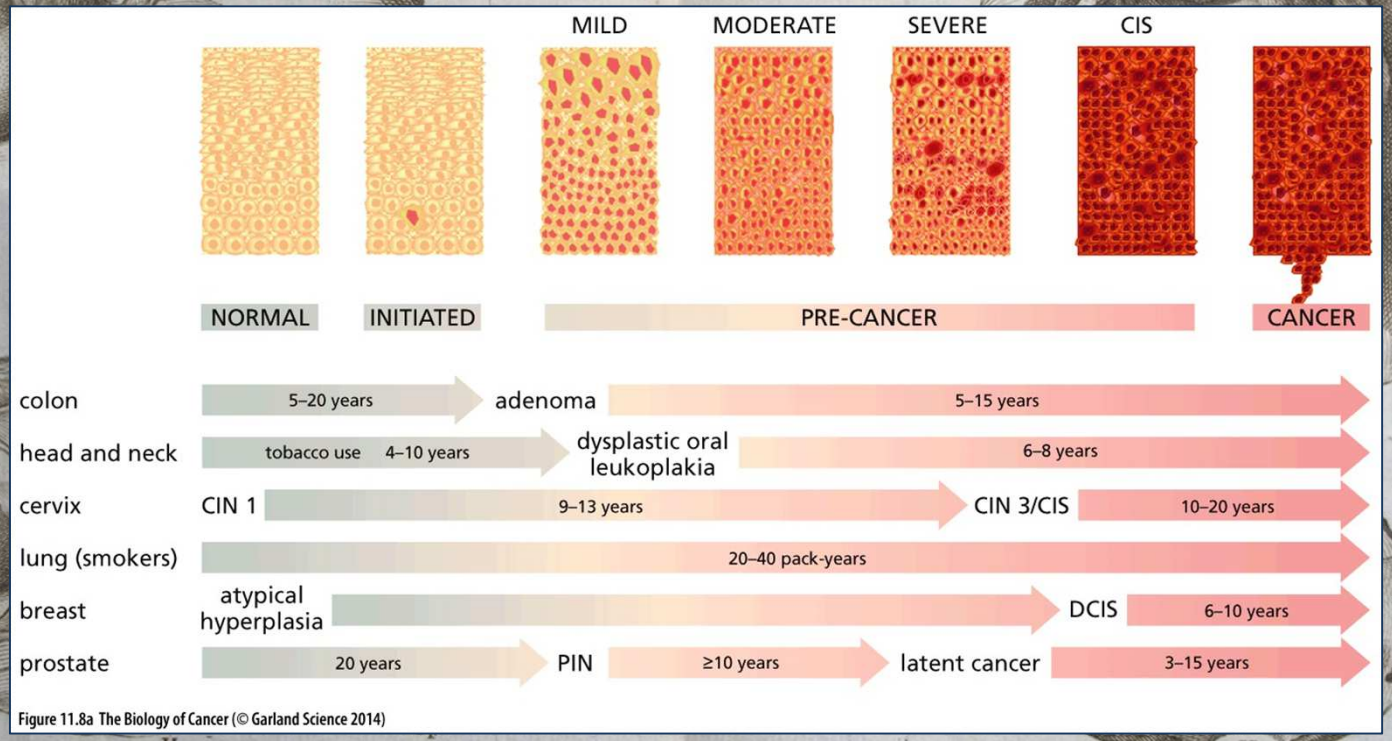
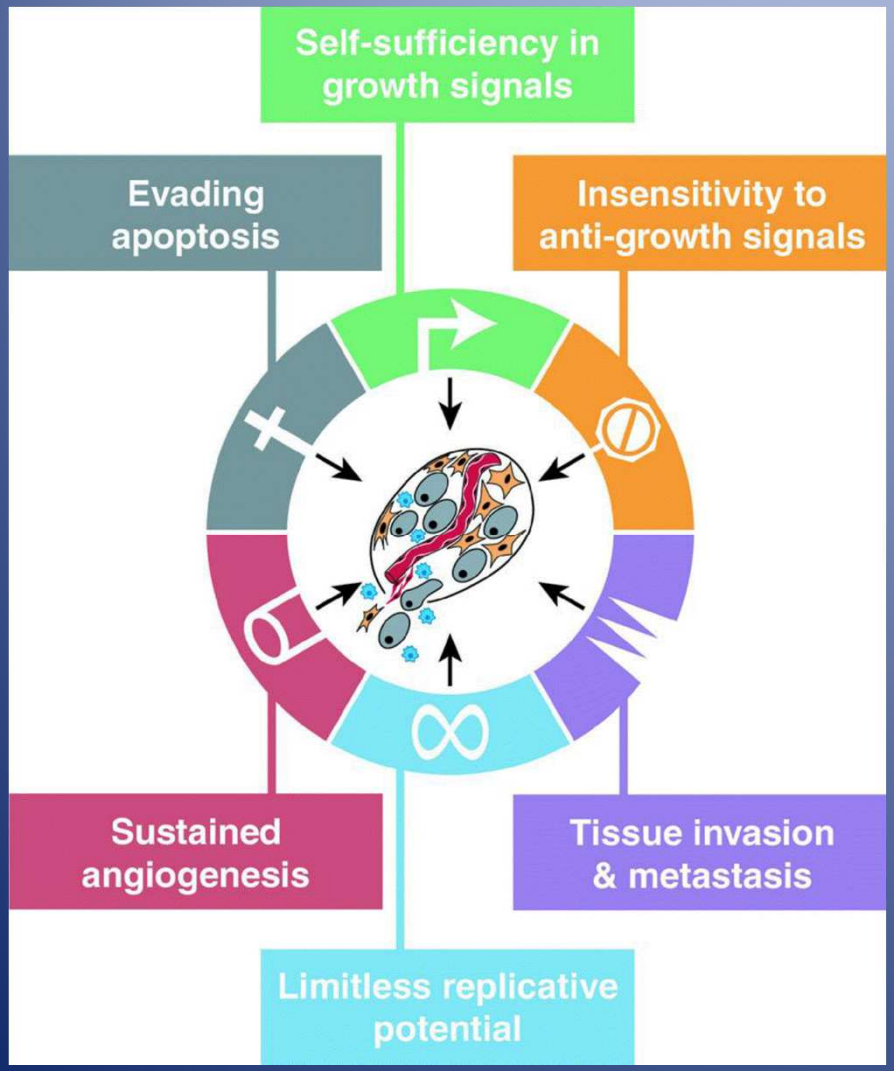
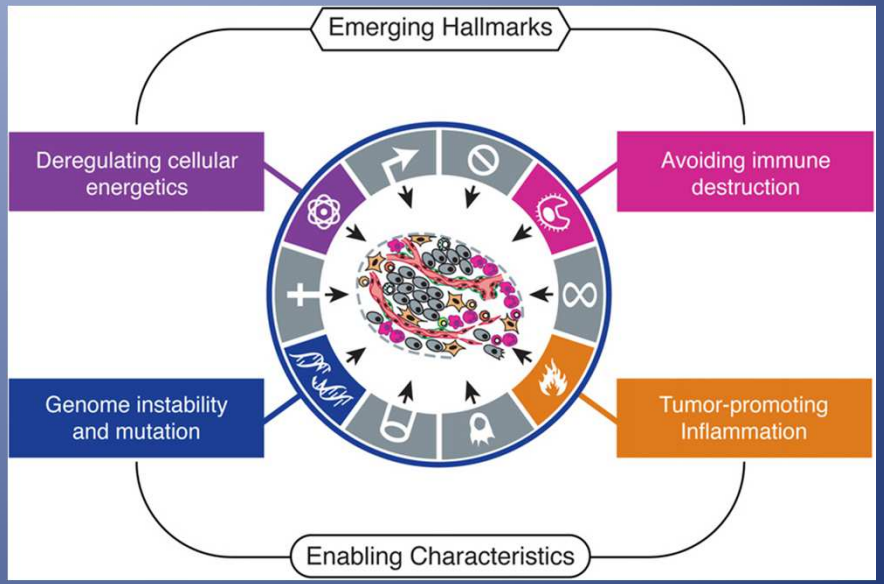


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

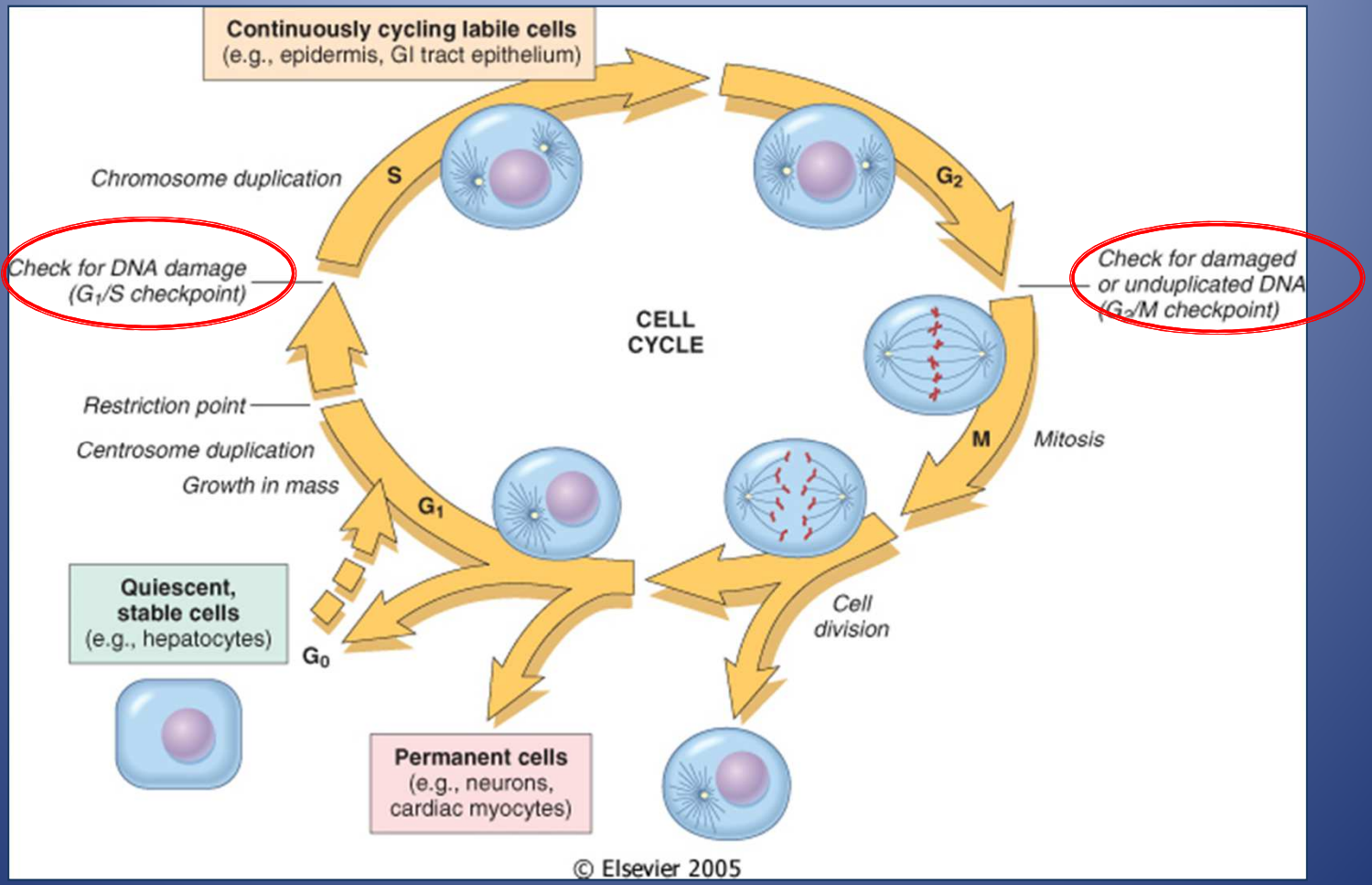
The tumor hallmarks

(Hanahan and Weinberg, 2000, 2011)

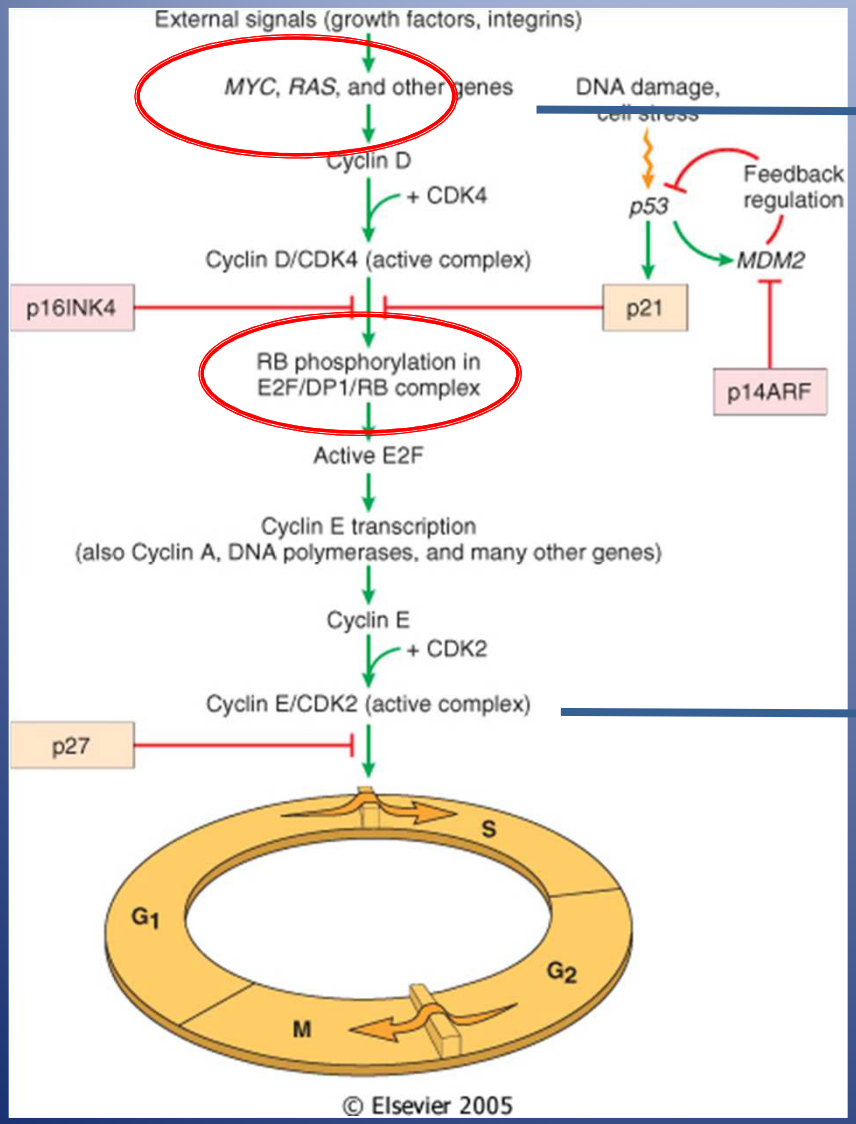


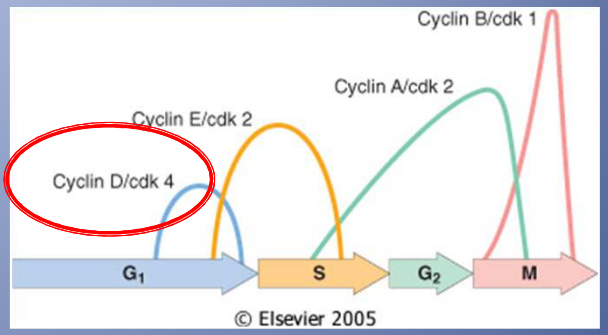


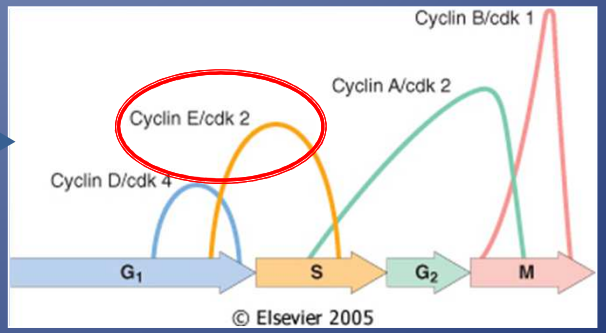
A step back inside the cell…



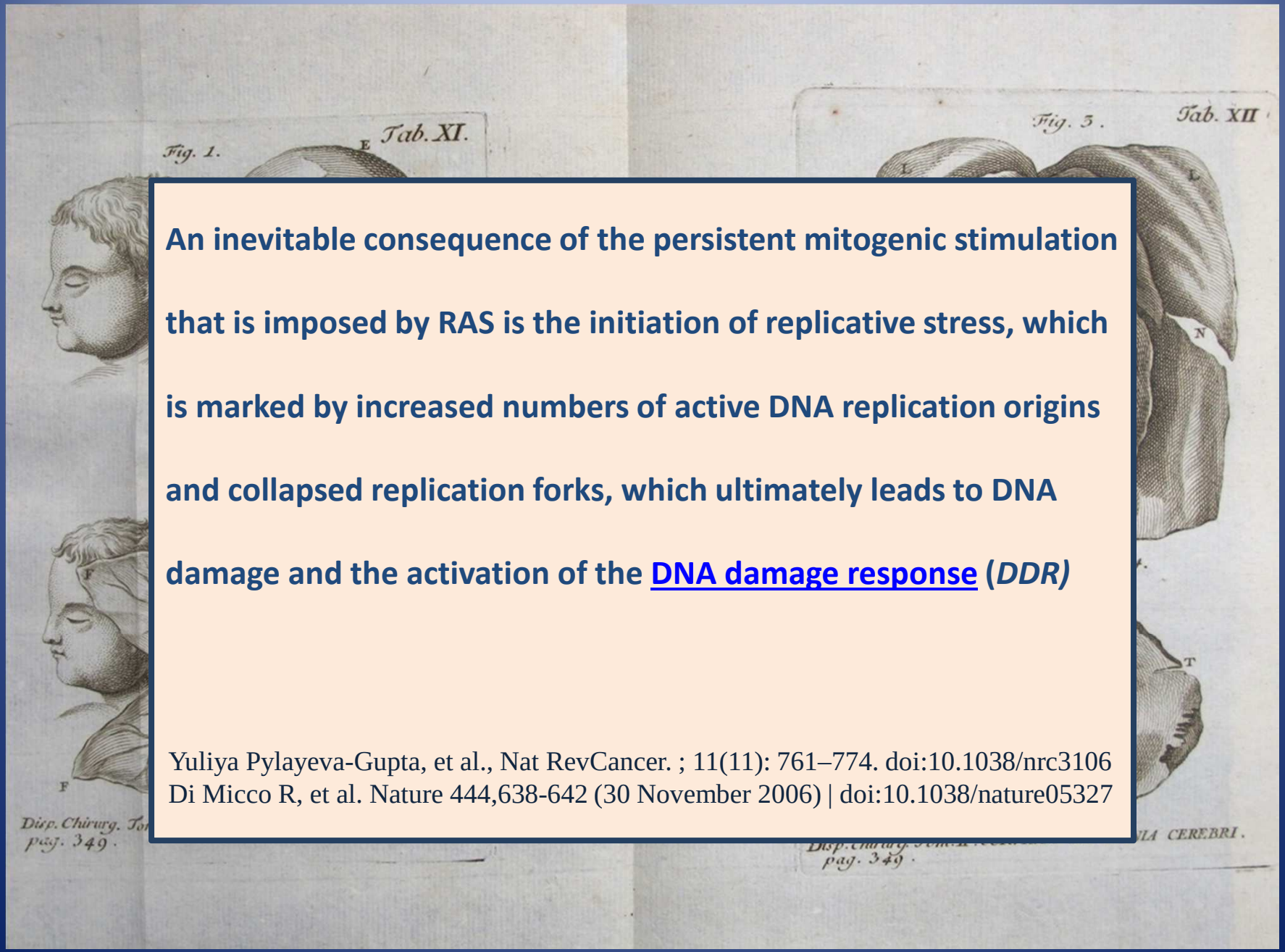
Genes involved in cell cycle regulation







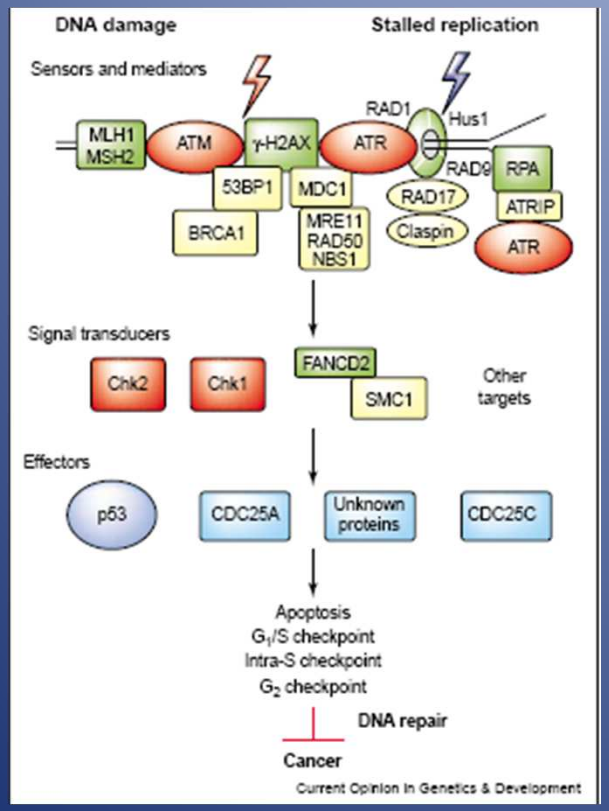
Dr. Jekyll and Mr. Hyde in cell cycle regulation



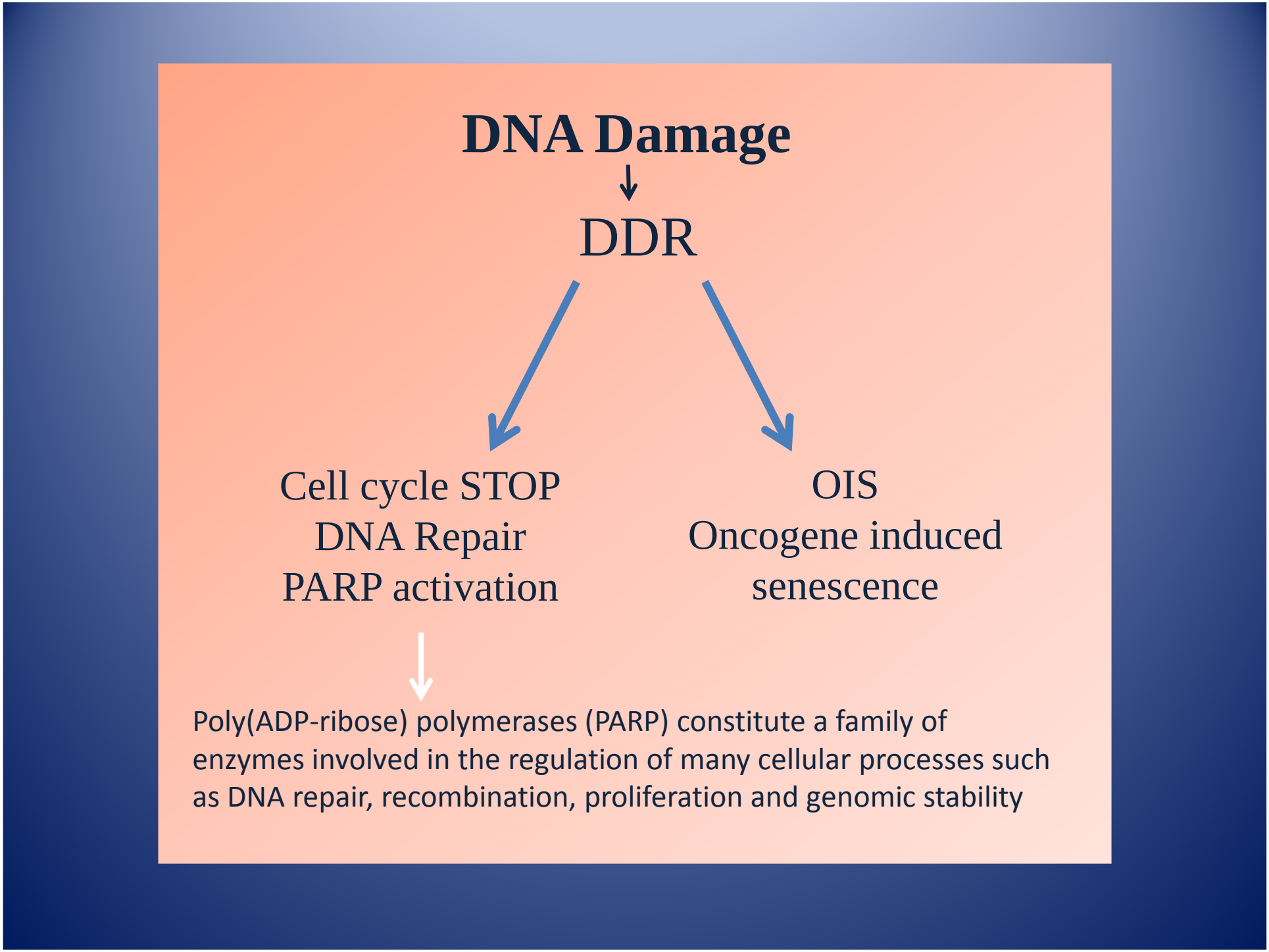
An inevitable consequence of the persistent mitogenic stimulation that is imposed by RAS is the initiation of replicative stress, which is marked by increased numbers of active DNA replication origins and collapsed replication forks, which ultimately leads to DNA damage and the activation of the DNA damage response (*DDR)*

Yuliya Pylayeva-Gupta, et al., Nat RevCancer. ; 11(11): 761–774. doi:10.1038/nrc3106
Di Micco R, et al. Nature 444,638-642 (30 November 2006) | doi:10.1038/nature05327

In a cell that possesses the full complement of functional DNA damage checkpoints, the engagement of the DDR by oncogenic genes as $HRAS^{G12V}$ leads to an irreversible cell cycle arrest that is known as oncogene-induced senescence (OIS)



Chris J Norbury, et al., Oncogene (2004) 23,2797–2808. doi:10.1038 –
Noboru Motoyama, et al., Current Opinion in Genetics& Development Volume 14, Issue 1, February 2004, Pages 11–16|doi:10.1016/j.gde.2003.12.003


DNA Damage
DDR
Cell cycle STOP
DNA Repair
PARP activation
OIS
Oncogene induced
senescence
Poly(ADP-ribose) polymerases (PARP) constitute a family of enzymes involved in the regulation of many cellular processes such as DNA repair, recombination, proliferation and genomic stability

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Methylation of PARP-1 promoter involved in the regulation of benzene-induced decrease of PARP-1 mRNA expression

Interference by Toxic Metal Ions with DNA Repair Processes and Cell Cycle Control: Molecular Mechanisms

A. Hartwig,[1] M. Asmuss,[1,2] I. Ehleben,[1] U. Herzer,[1] D. Kostelac,[1] A. Pelzer,[1] T. Schwerdtle,[1] and A. Bürkle[3]

[1]Institut für Lebensmittelchemie und Toxikologie, Universität Karlsruhe, Karlsruhe, Germany; [2] Bundesamt für Strahlenschutz, Institut für Strahlenhygiene, Neuherberg, Germany; [3]Department of Gerontology, University of Newcastle, Newcastle upon Tyne, United Kingdom

NATURE GENETICS VOLUME 34 | NUMBER 3 | JULY 2003

Cancer, cadmium and genome integrity

Cynthia T McMurray & John A Tainer

The direct inhibition of DNA mismatch repair by cadmium provides a molecular mechanism for cadmium toxicity with profound implications for human health, risk assessment and biological understanding of environmental mutagens. Alteration of key DNA damage response pathways may prove even more important than direct DNA damage by mutagens.

a

Corel royalty-free art photo image 523028

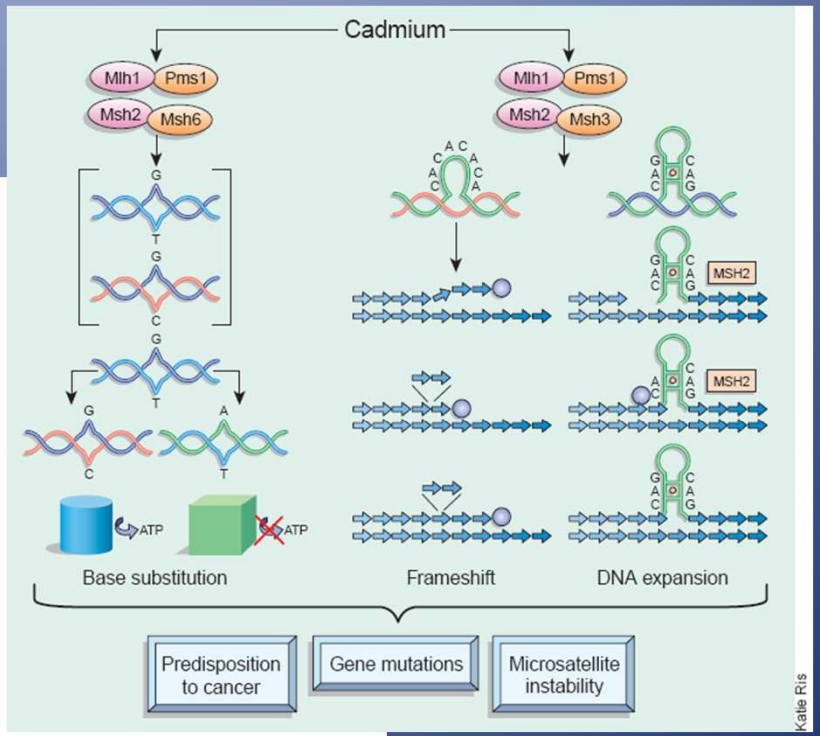
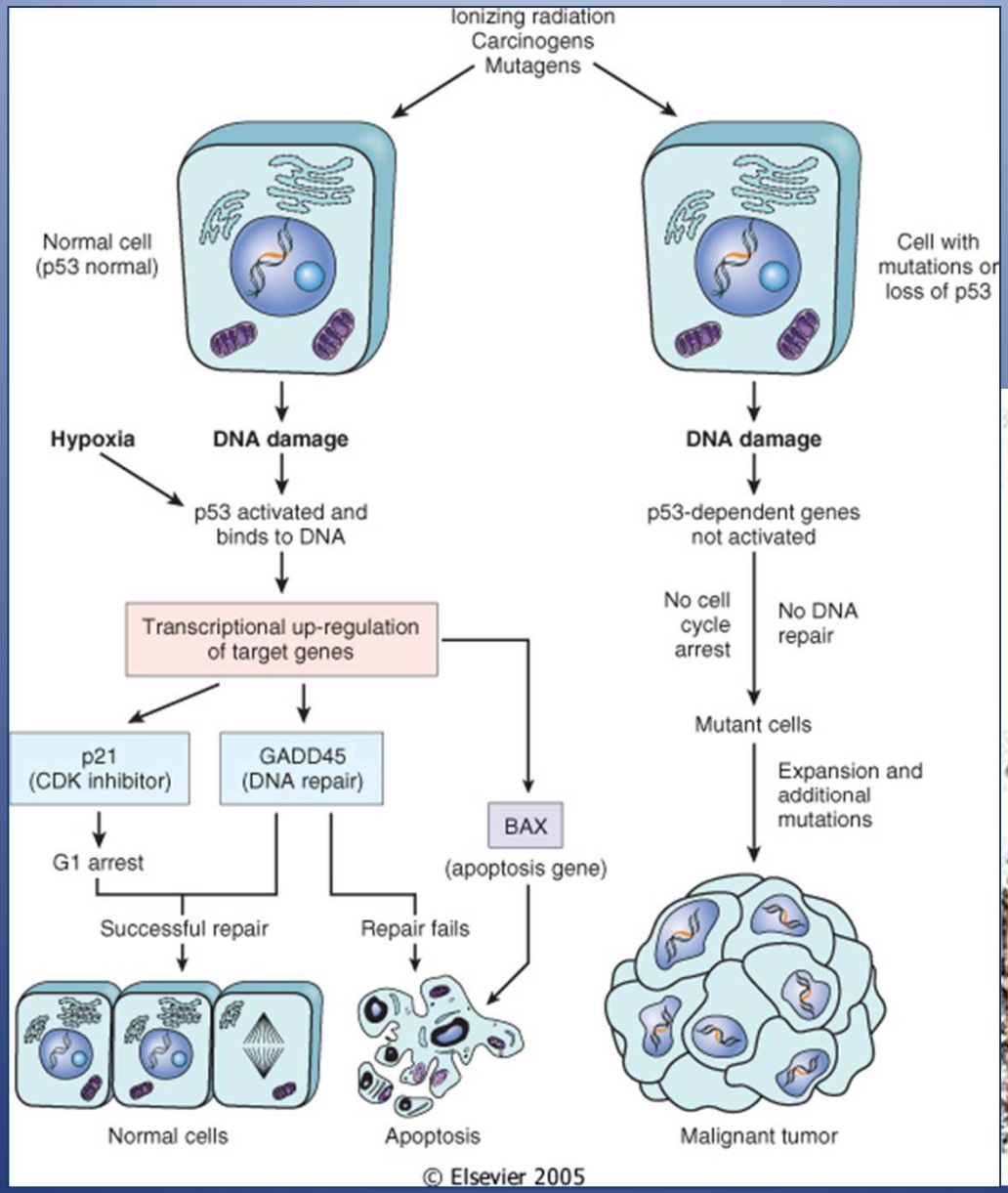
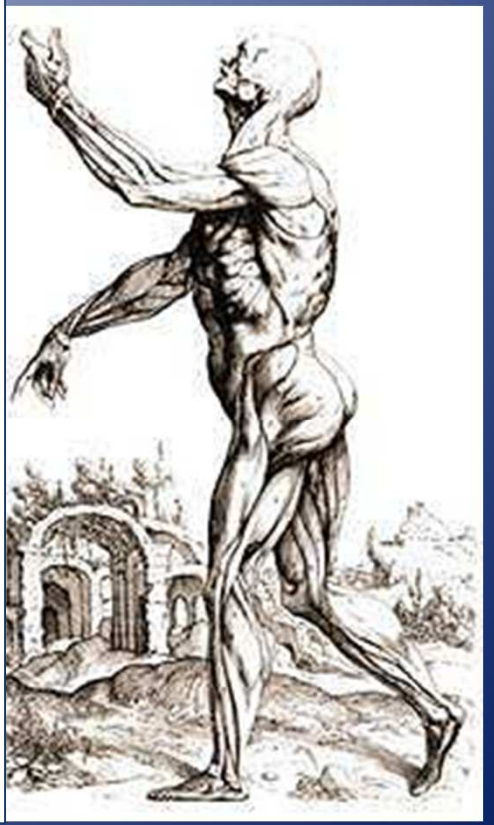


Figure 1 A beautiful toxin. (**a**) Claude Monet's *Fisherman's Cottage on the Cliffs at Varengeville* from 1882 showing the powerful use of cadmium yellow pigments. (**b**) Revertant yeast colonies reflect mutagenesis induced by cadmium inhibition of DNA MMR.

The essential role of p53





Int. J. Cancer: **122,** 2154–2159 (2008)

SHORT REPORT

COX-2 and p53 in human sinonasal cancer: COX-2 expression is associated with adenocarcinoma histology and wood-dust exposure

Reetta Holmila[1], Diane Cyr[2], Danièle Luce[2], Pirjo Heikkilä[1], Michael Dictor[3], Torben Steiniche[4], Tuula Stjernvall[1], Jette Bornholdt[5], Håkan Wallin[5], Henrik Wolff[1,6] and Kirsti Husgafvel-Pursiainen[1]*

Polycyclic aromatic hydrocarbons (PAH)

MODE OF ACTION (MOA) or simply marker research?

Zuo et al. BMC Genomics 2014, 15:880
http://www.biomedcentral.com/1471-2164/15/880

BMC Genomics

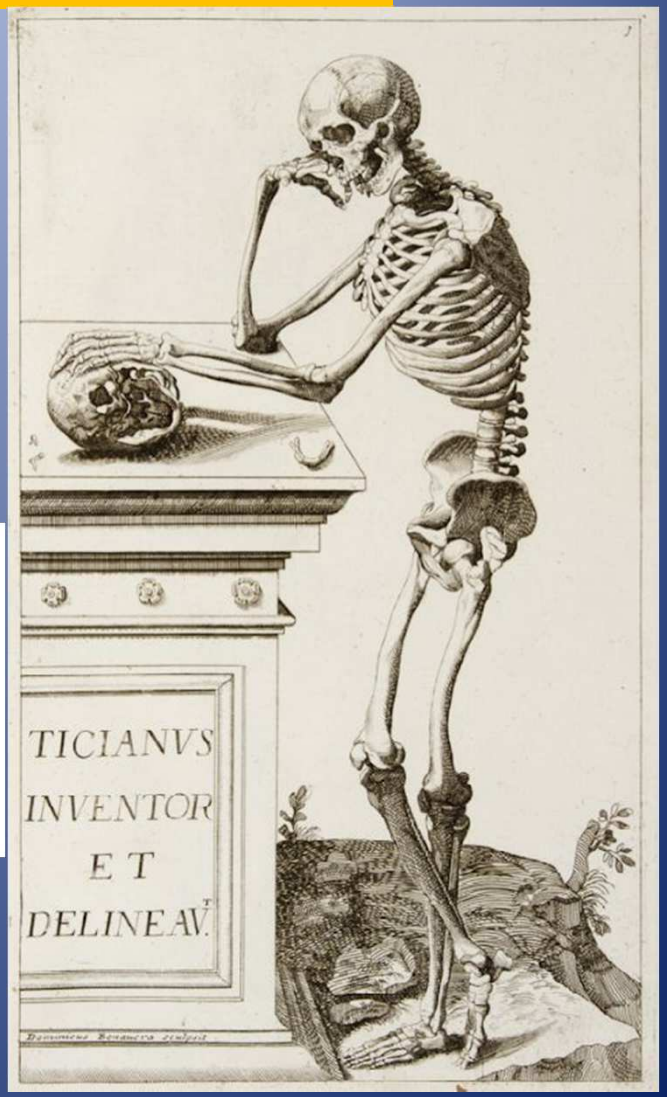
RESEARCH ARTICLE Open Access

Benzo[*a*]pyrene-induced DNA adducts and gene expression profiles in target and non-target organs for carcinogenesis in mice

Jie Zuo[1], Daniel S Brewer[2], Volker M Arlt[3], Colin S Cooper[4] and David H Phillips[3*]

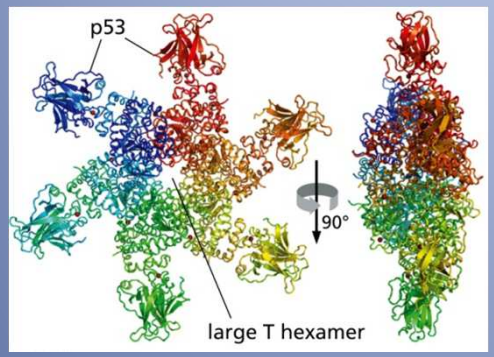
The EMBO Journal (2007) 26, 2923–2932 | © 2007 European Molecular Biology Organization | All Rights Reserved 0261-4189/07
www.embojournal.org

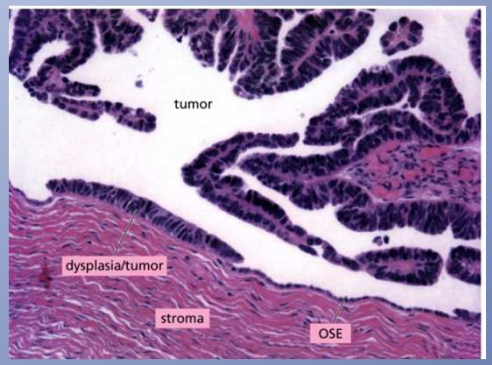
The human DNA repair factor XPC-HR23B distinguishes stereoisomeric benzo[*a*]pyrenyl-DNA lesions



Vincent **Mocquet, et al**
DOI 10.1038/sj.emboj.7601730 |Published online 24.05.2007The EMBO Journal(2007)26,2923-2932

Papova virus lead to the discovery of p53



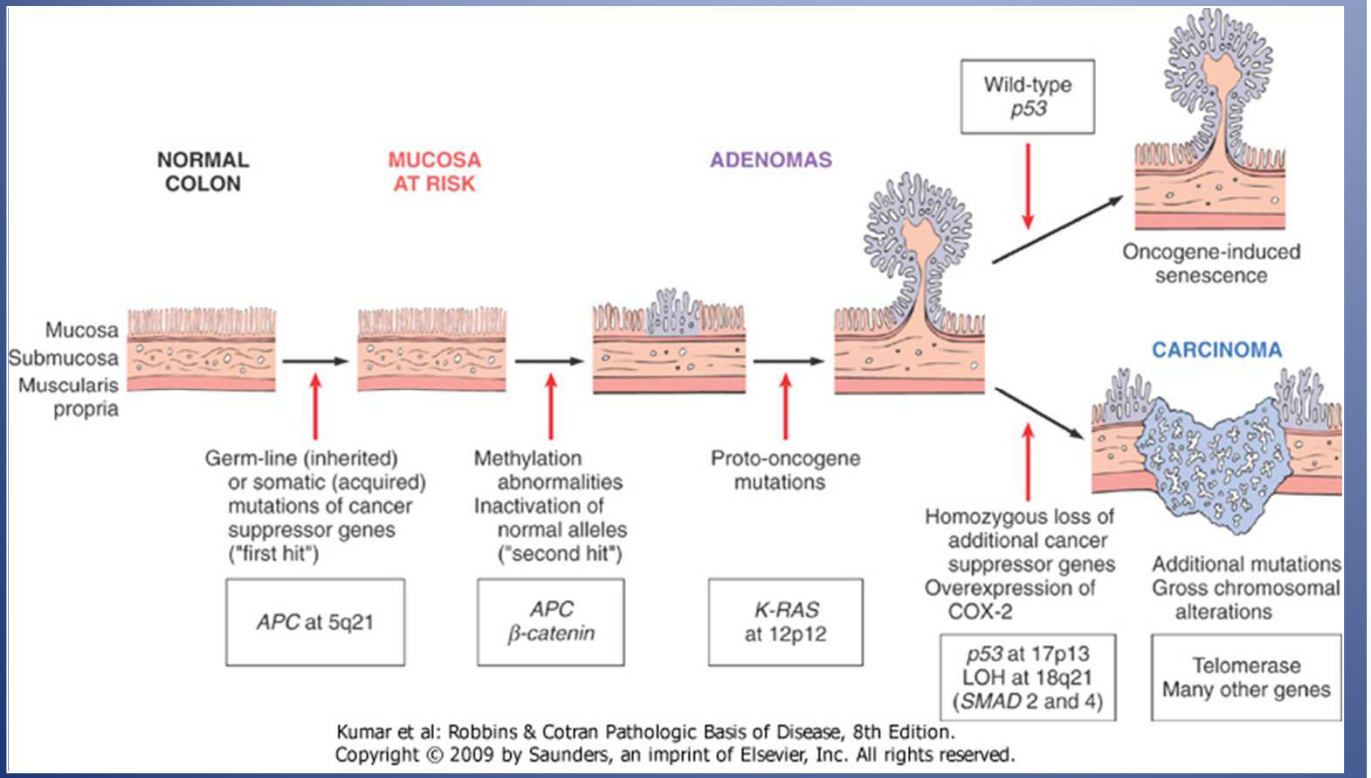


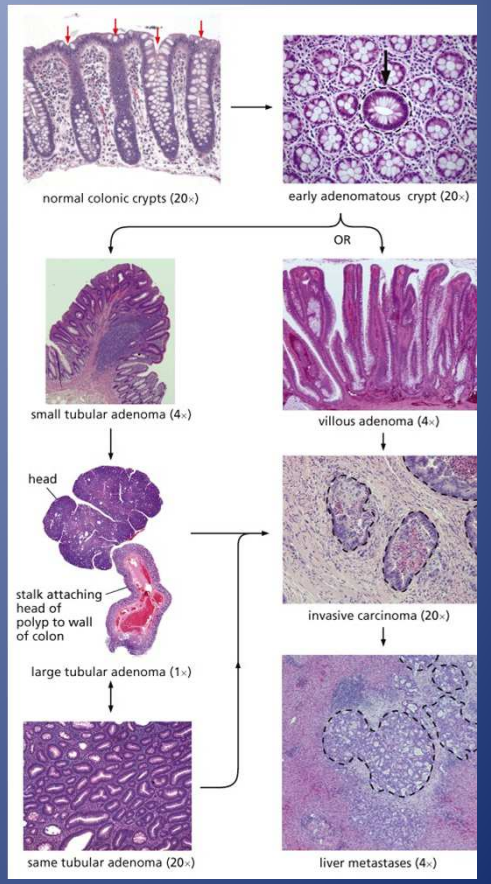
and other oncosopressor genes...

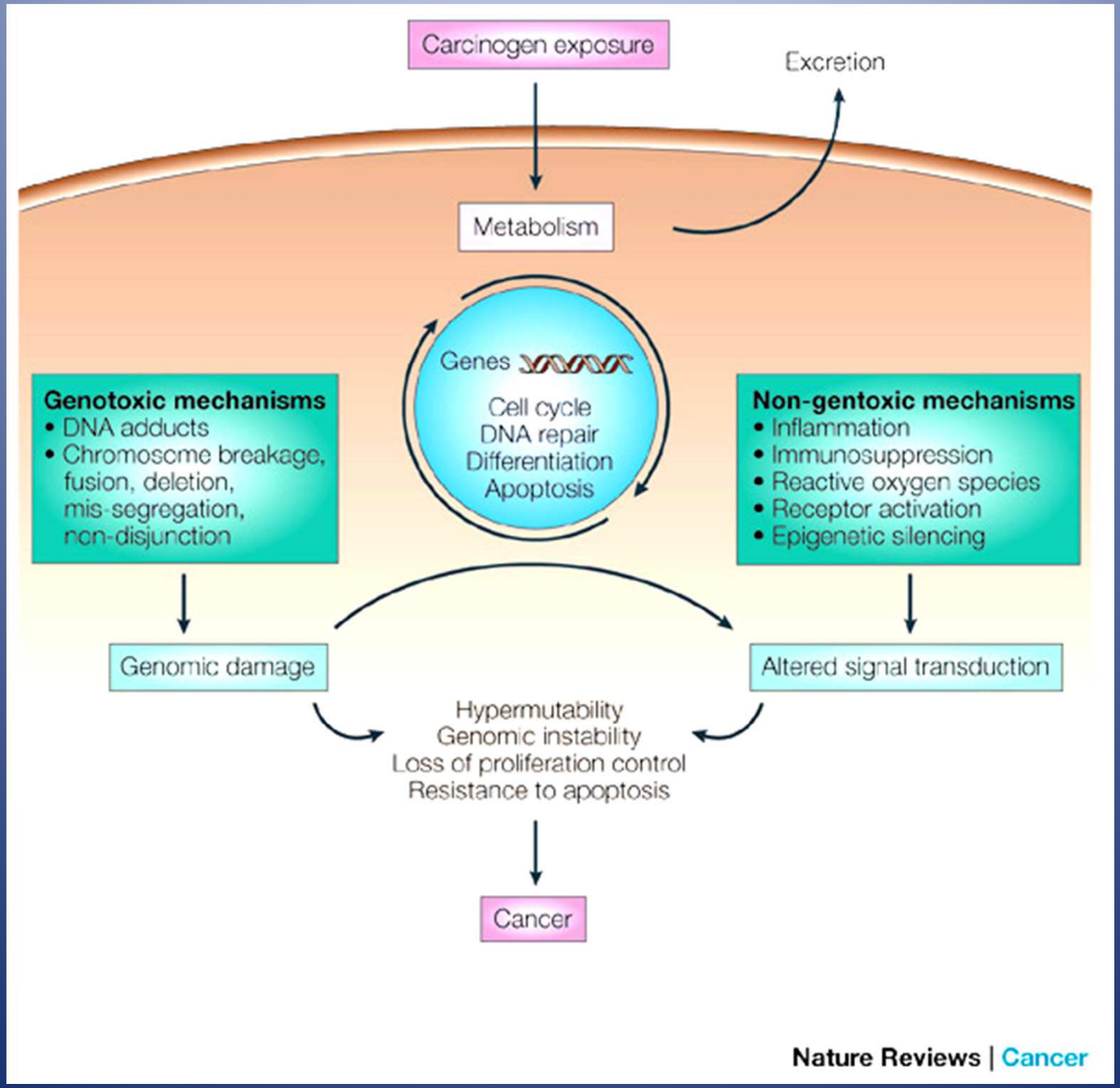
Tumor viruses that perturb pRb, p53, and/or apoptotic function

Virus	Viral protein targeting pRb	Viral protein targeting p53	Viral protein targeting apoptosis
SV40	large T (LT)[a]	large T (LT)[a]	
Adenovirus	E1A	E1B55K	E1B19K[b]
HPV	E7	E6	
Polyomavirus	large T	large T?	middle T (MT)[c]
Herpesvirus saimiri	V cyclin[d]		v-Bcl-2[e]
HHV-8 (KSHV)	K cyclin[d]	LANA-2	v-Bcl-2,[e] v-FLIP[f]
Human cytomegalovirus (HCMV)	IE72[g]	IE86	vICA,[h] pUL37[i]
HTLV-I	Tax[j]	Tax	
Epstein–Barr	EBNA3C	EBNA-1[k]	LMP1[k]

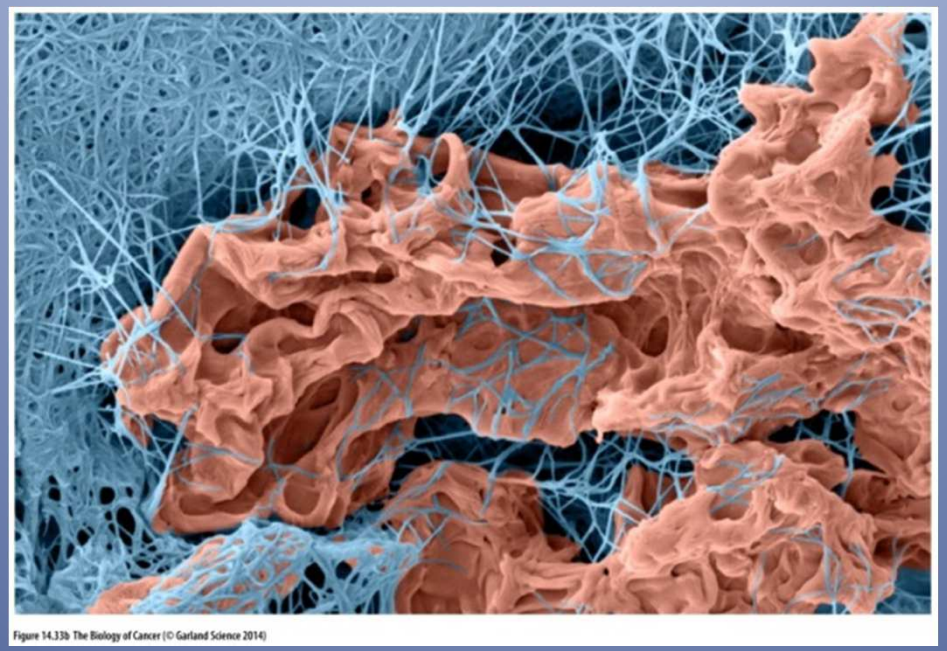
Transformation usually requires collaboration of two or more mutated genes: a multi-step transformation model





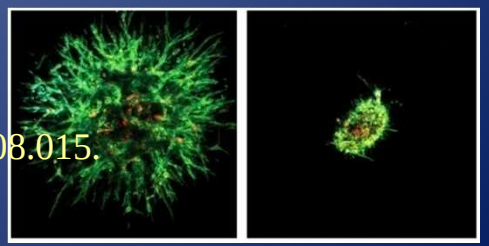

Carcinogen exposure
Excretion
Metabolism
Genes
Cell cycle
DNA repair
Differentiation
Apoptosis
Genotoxic mechanisms
• DNA adducts
• Chromosome breakage, fusion, deletion, mis-segregation, non-disjunction
Non-gentoxic mechanisms
• Inflammation
• Immunosuppression
• Reactive oxygen species
• Receptor activation
• Epigenetic silencing
Genomic damage
Altered signal transduction
Hypermutability
Genomic instability
Loss of proliferation control
Resistance to apoptosis
Cancer
Nature Reviews | Cancer

The Extracellular Matrix (EM) pressure



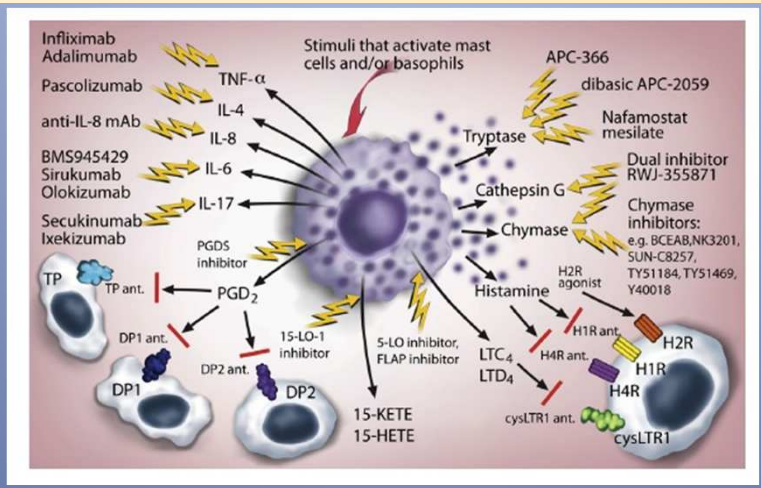
Fibrosarcoma cells invading collagen fibers

Chronic inflammation promotes tumor progression trough TGF-β EM deposition and TNF-α *myc* (proliferation) and anti-apoptotic signalling activation. The stiff EM induces integrin clustering and gene expression changes *vs* invasion trough YAP/TAZ transcription factor coactivators..



Michael W Pickup et al EMBO reports Vol 15 | No 12 | 2014
Hongmei Yu et al. Trends Cell Biol. 2011 January ; 21(1): 47–56. doi:10.1016/j.tcb.2010.08.015.

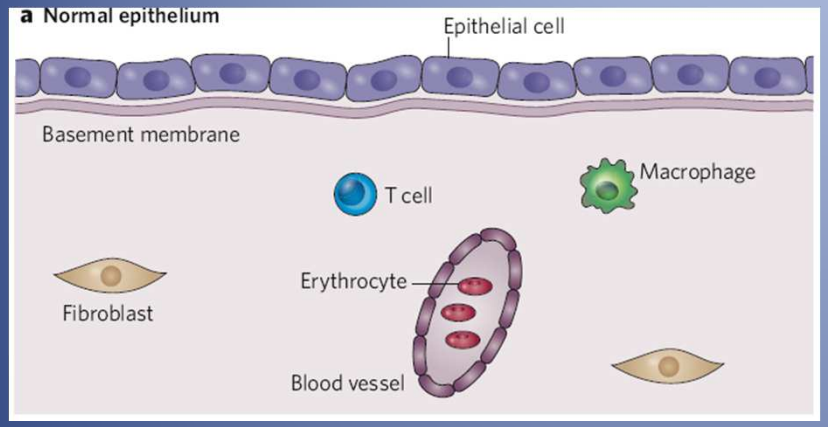
The key role of mastocytes in chronic inflammation and fibrosis Not enough investigated



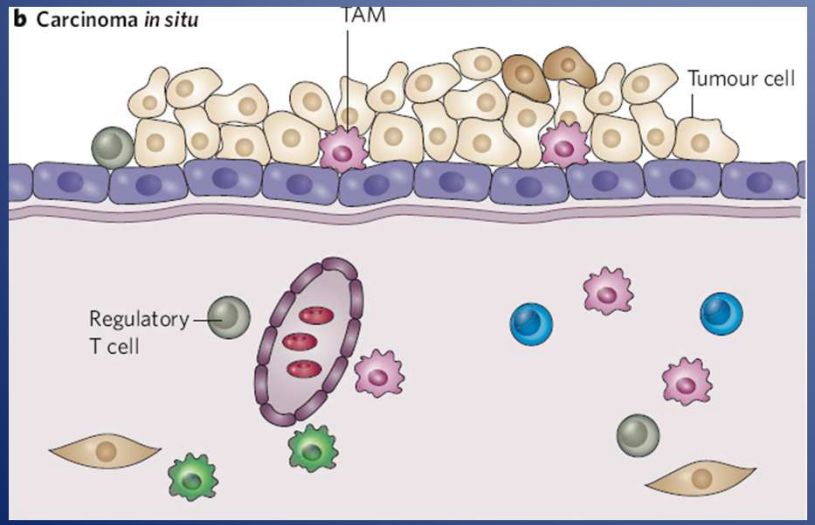
Chronic inflammation and excess of extracellular matrix can be observed in a variety of tumors.

Mast cell vesicles not only support a profibrotic Th-2–response, they also contain directly profibrotic stimuli such as transforming growth factor (TGF)-beta, platelet derived growth factor (PDGF) or granulocyte macrophage colony-stimulating factor (GM-CSF) that further induce tumor cells proliferation, de-differentiation and movement.

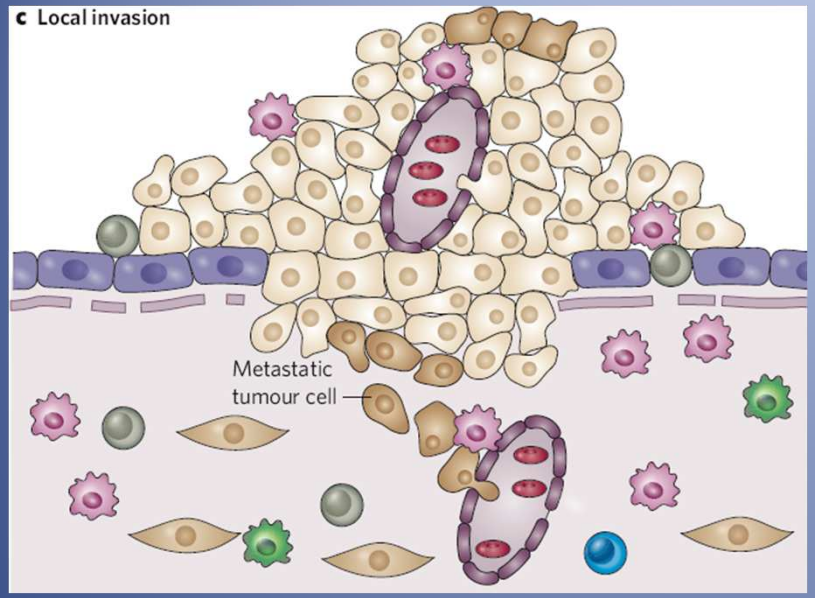
Moving out: invasion and metastasis: the inflammosoma is essential to drive invasion



Normal epithelium

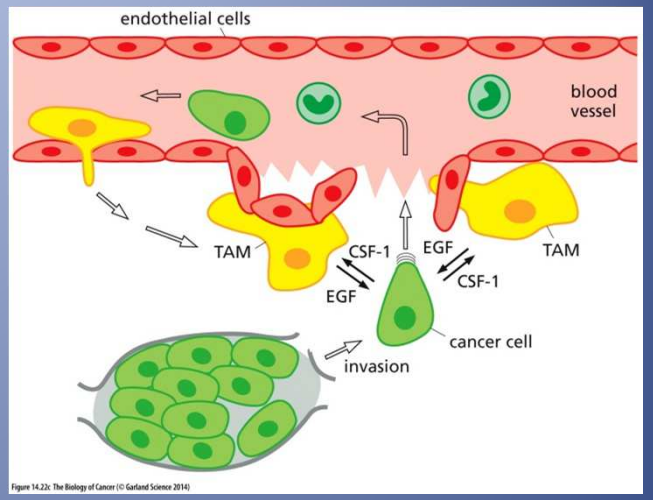


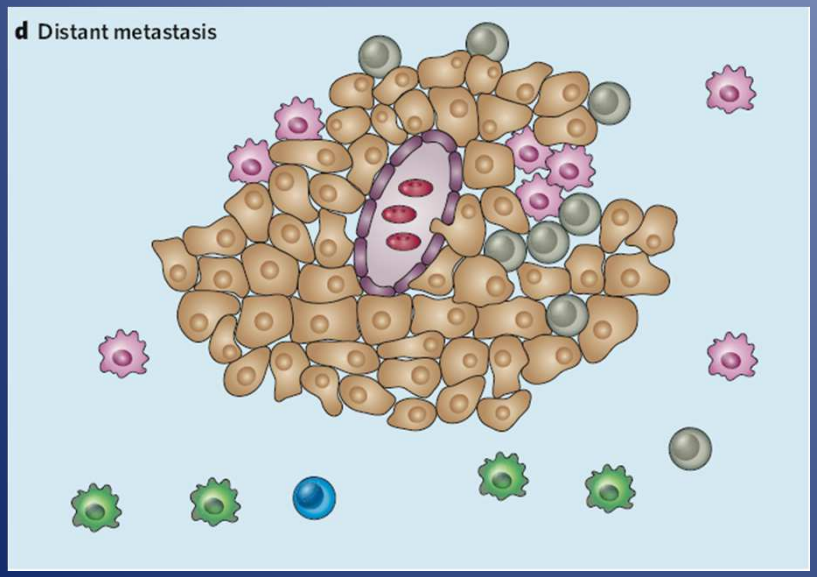
Carcinoma *in situ*. External signals (inflammatory) and oncogenic signals inside the cells induce chemokines, cytokines, secretion, tumor associated macrophages (TAM) and T-linfocytes chemotaxis. In parallel cancer cells express cytokines receptors.



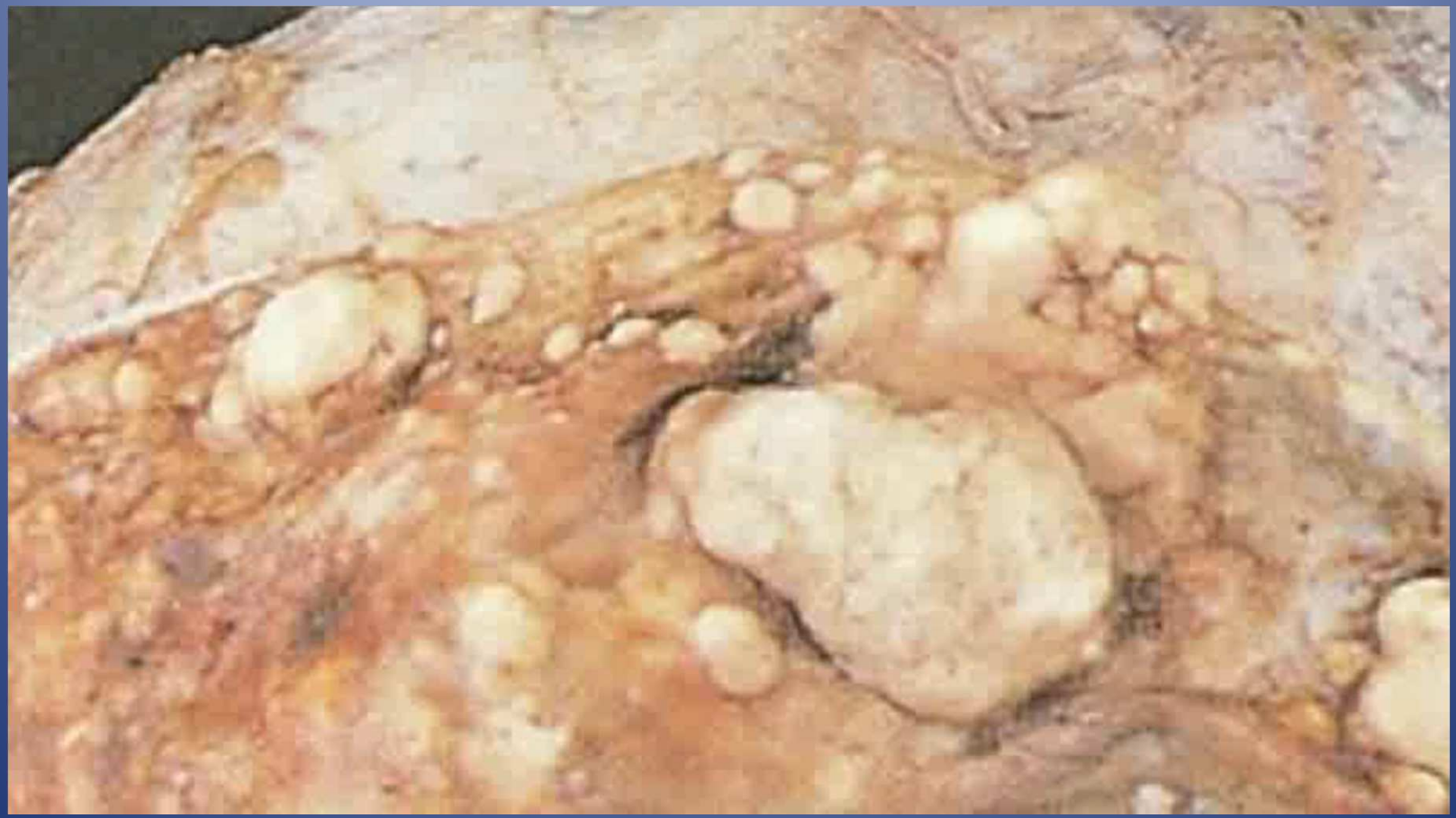
Local invasion

Intravasation





Distant metastasis.



Chronic inflammation milieu induced by chronic hepatitis B and C virus Leads to hepatocellular carcinoma (HCC)

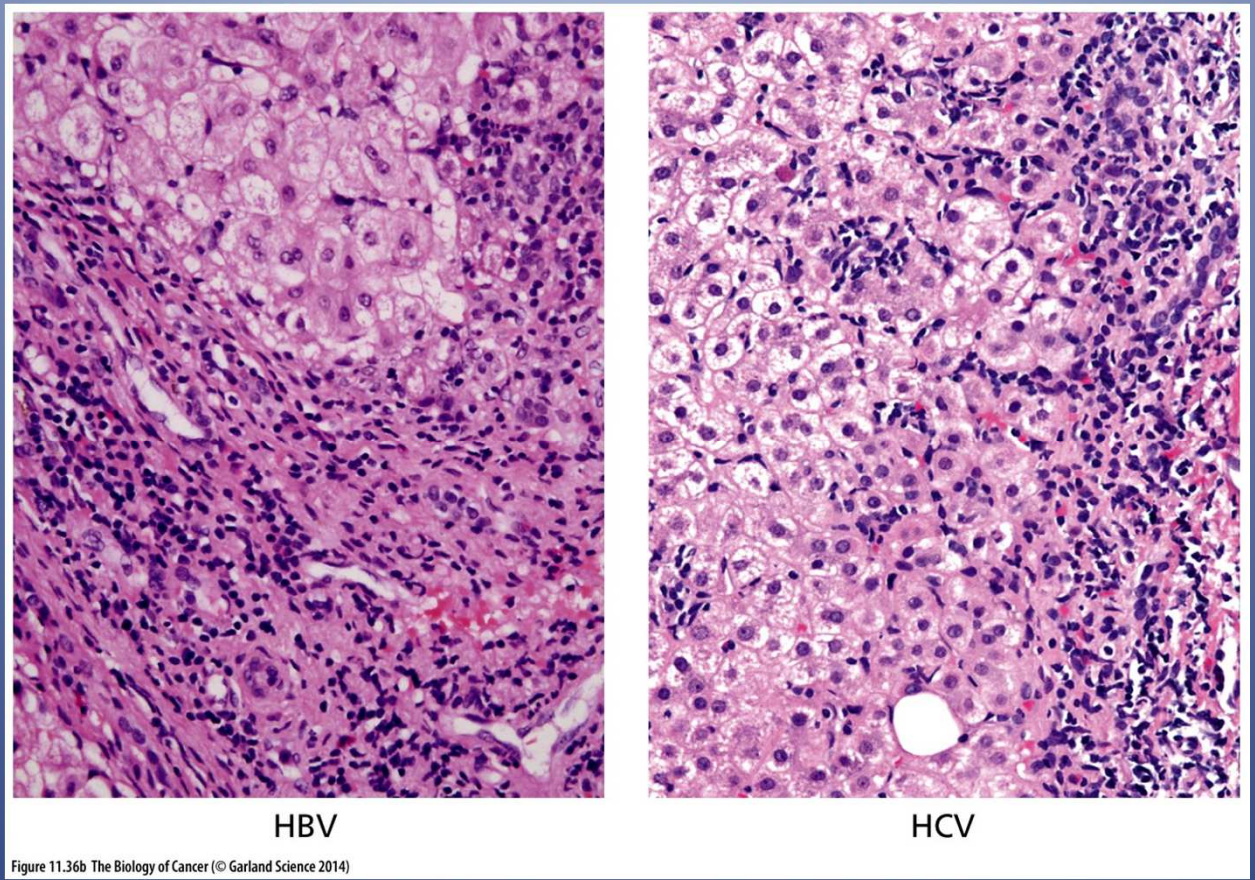
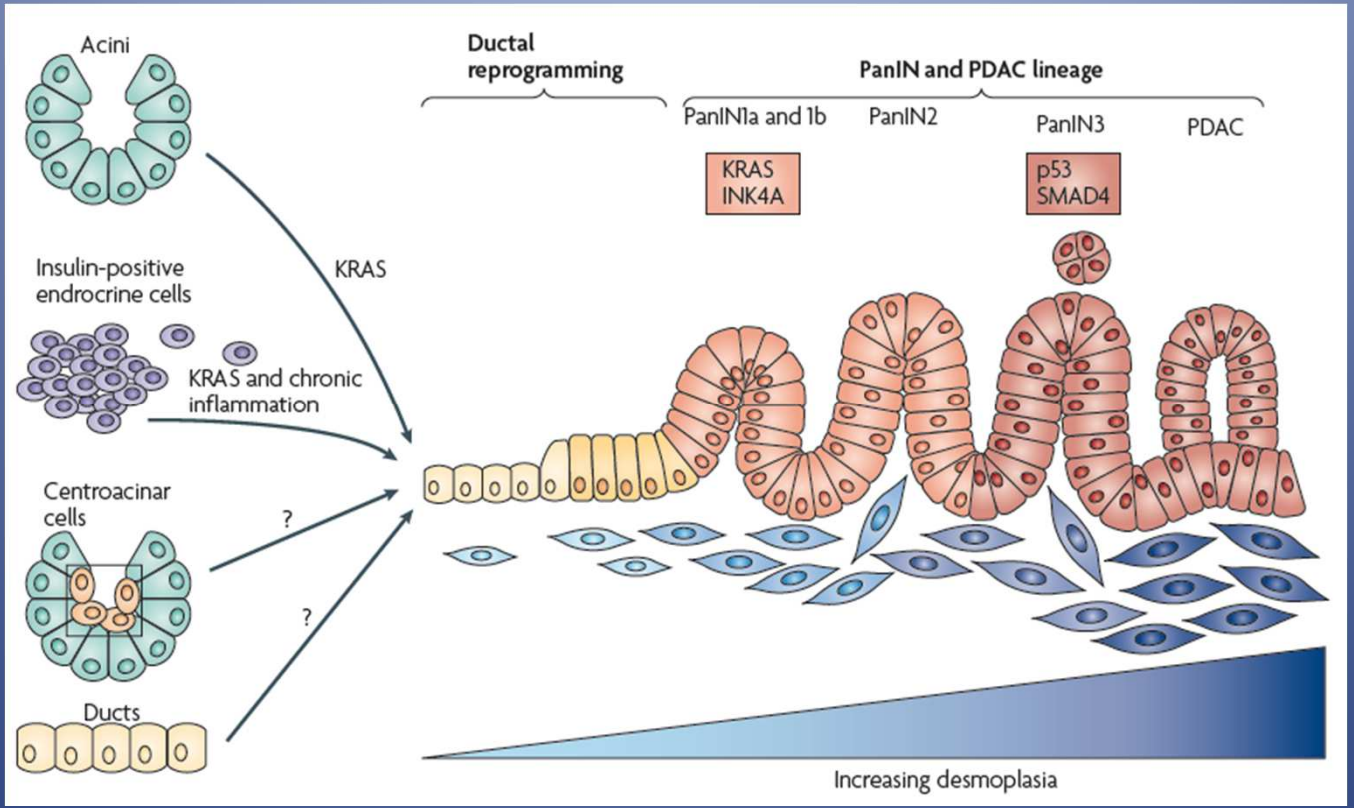


Figure 11.36b The Biology of Cancer (© Garland Science 2014)

The inflammatory states rather then specific aspects of viral function are responsible of HCC

KRAS is a master regulator of pancreatic ductal adenocarcinoma initiation and progression.



Epigenetic regulation of gene expression

Gene expression regulation by methylation

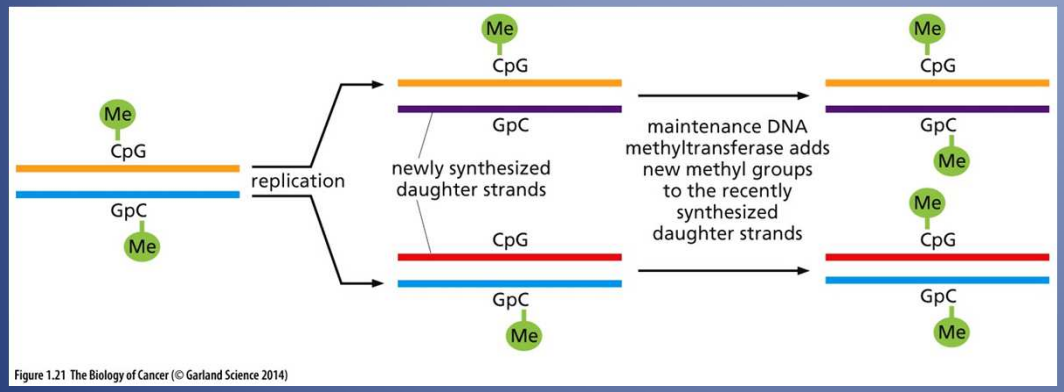
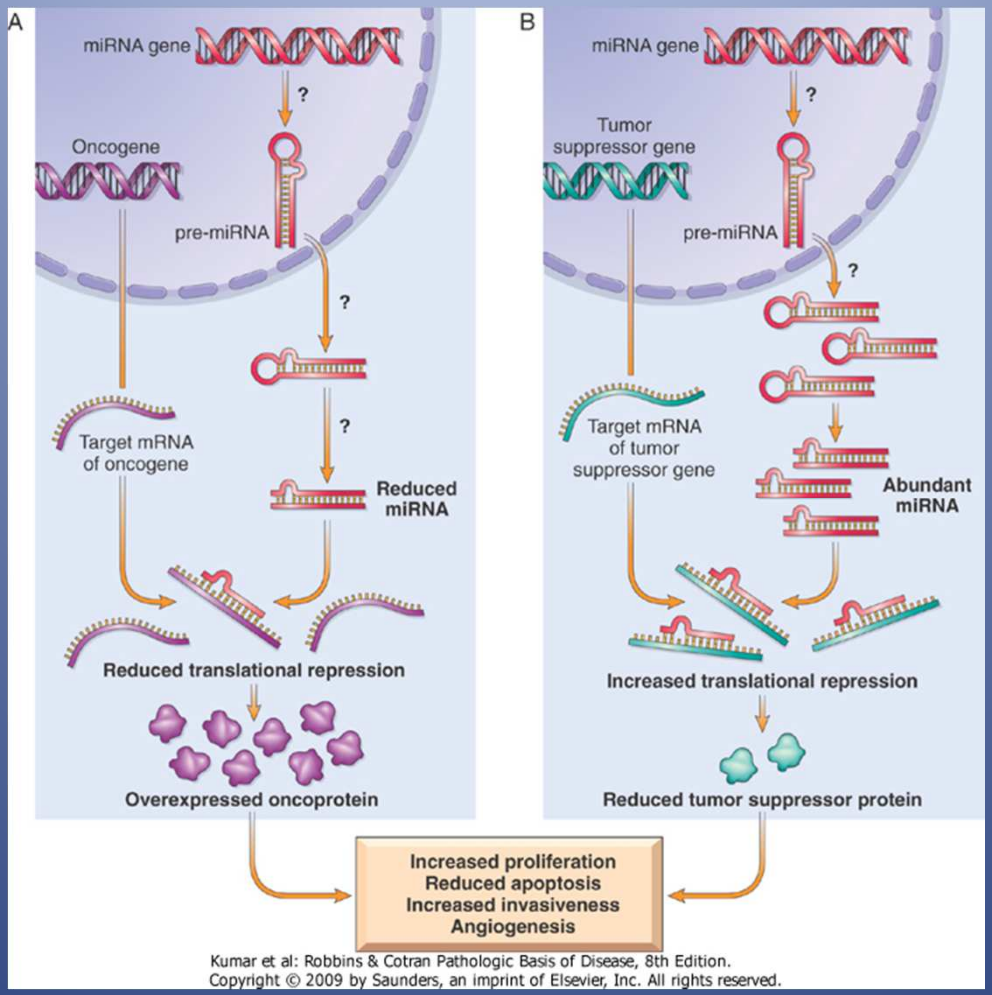


Figure 1.21 The Biology of Cancer (© Garland Science 2014)

RNA Trasduction regulation by miRNA



The effects of environmental chemical carcinogens on the microRNA machinery

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[b] *Mutagenesis Unit, IRCCS University Hospital San Martino – IST National Research Cancer Institute, Genoa, Italy*

	Human	Left ventriculum endocardium	qRT-PCR	miR-1↑	Yang et al., 2007
	Mice	Heart	qRT-PCR	miR-1↑	Yang et al., 2007
Metal rich fumes in steel industry (particulate matter, PM10)	Human	Blood lymphocytes	Microarray, qPCR	miR-21↑, miR-146↓, miR-222↑	Bollati et al., 2010
	In vitro	Human endothelial cells	Microarray, qPCR	miR-221↑, miR-222↑	Suarez et al., 2007
	Rat	Cardiac myocytes	qPCR	miR-21↑	Cheng et al., 2009
Black carbon and coal dust (urban traffic particulate matter)	Human	Blood samples	Microarray, qPCR	let-7g↑, miR-29↑, miR-146↑, miR-421↑	Motta et al., 2013
	Human	Blood lymphocytes	SNPs genotyping	SNPs in miRNA processing genes (DICER, DGCR8 (interacting with DROSHA to cleave pri-miRNA), Gemin3/4 (guiding miRNA into RISC) associated with high arterial pressure	Wilker et al., 2010
Silica dust	Rat	Lung tissue	Microarray, qPCR	let-7d↓, let-7f↓, miR-17-1-3p↑, miR-22↑, miR-25↓, miR-26a↓, miR-26b↓, miR-28↓, miR-29c↓, miR-30a↓, miR-30c↓, miR-30d↓, miR-96↑, miR-98↓, miR-99a↓, miR-101a↓, miR-126↓, miR-138-1↑, miR-140↓, miR-141↑, miR-144↓, miR-145↓, miR-146↑, miR-181b↓, miR-182↑, miR-183↑, miR-200b↓, miR-204↑, miR-299↑, miR-300-5p↑, miR-344b↑, miR-345-5p↓ miR-352↓, miR-375↓, miR-322↓, miR-505↓, miR-675↑	Faxuan et al., 2012
Coal fumes (miners)	Human	Blood lymphocytes	SNPs genotyping	SNPs in pre-miRNA genes of miR-149 associated with pneumoconiosis	Wang et al., 2010a
RDX (explosive industry, mining, building, etc.) in water	Mouse	Brain	Microarray, qPCR	miR-10b↓, miR-15↑, miR-206↑, miR-497↑	Zhang and Pan, 2009
	Mouse	Liver	qPCR	let-7e↓, miR-15↑, miR-29c↑, miR-30e↑, miR-574↓, miR-466f↓, miR-689↑, miR-802↑	Zhang et al., 2007
Dimethylhydrazine	Rat	Colon, mucosa cells	Microarray, qPCR	miR-21↑	Nautiyal et al., 2012
Benzo[a]pyrene	In vitro	Human bronchial epithelial cells	Microarray, qPCR	miR-10a↓, miR-106a↑, miR-129↑, miR-320↑, miR-363↓, miR-493↓, miR-494↑, miR-498↑	Shen et al., 2009
	In vitro	Human bronchial epithelial cells	Microarray, qPCR	miR-506a↑	Zhao et al., 2011a
	In vitro	Human bronchial epithelial cells	qPCR	miR-106a↑	Jiang et al., 2011
	In vitro	Human bronchial epithelial cells	qPCR	miR-22↓	Liu et al., 2010b
	In vitro	Murine bronchial cells	Microarray, qPCR	miR-10a↓, miR-320↑, miR-494↑	Duan et al., 2010
	In vitro	Mouse lung	Microarray	miR-29b↑, miR-34b↑, miR-34c↑, miR-122↓, miR-142-5p↓, miR-150↓, miR-638↑	Halappanavar et al., 2011a
	In vitro	Human non-small-cell lung cancer, peripheral lymphocytes	miRNA array, qPCR	miR-638↑	Li et al., 2012a
	In vitro	Human hepatocellular carcinoma	miRNA array, qPCR	miR-29a↑, miR-99a↓, miR-139-3p↑, miR-197↑, miR-210↑, miR-294↑, miR-574-5p↑, miR-467f↑	Lizarraga et al., 2012
	In vitro	Lung cancer cells	qPCR	miR-346↓, miR-483↓, miR-466f-5p↓, miR-1896↓, miR-1906↓	Barkley and Santocanale, 2013
	In vitro	Mouse embryo	Microarray, qPCR	miR-290↑	Brevik et al., 2012
	In vitro	Liver tissue	Microarray, qPCR	miR-34a↑	Malik et al., 2012

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Environmental Toxicology DOI 10.1002/tox

miR-21 regulates *N*-methyl-*N*-nitro-*N*′-nitrosoguanidine-induced gastric tumorigenesis by targeting *FASLG* and *BTG2*

Qiaoyuan Yang[a], Enwu Xu[b], Jiabin Dai[a], Jianjun Wu[a], Shaozhu Zhang[a], Baoying Peng[a], Yiguo Jiang[a,*]

[a] *Institute for Chemical Carcinogenesis, State Key Laboratory of Respiratory Disease, Guangzhou Medical University, Guangzhou 510182, PR China*
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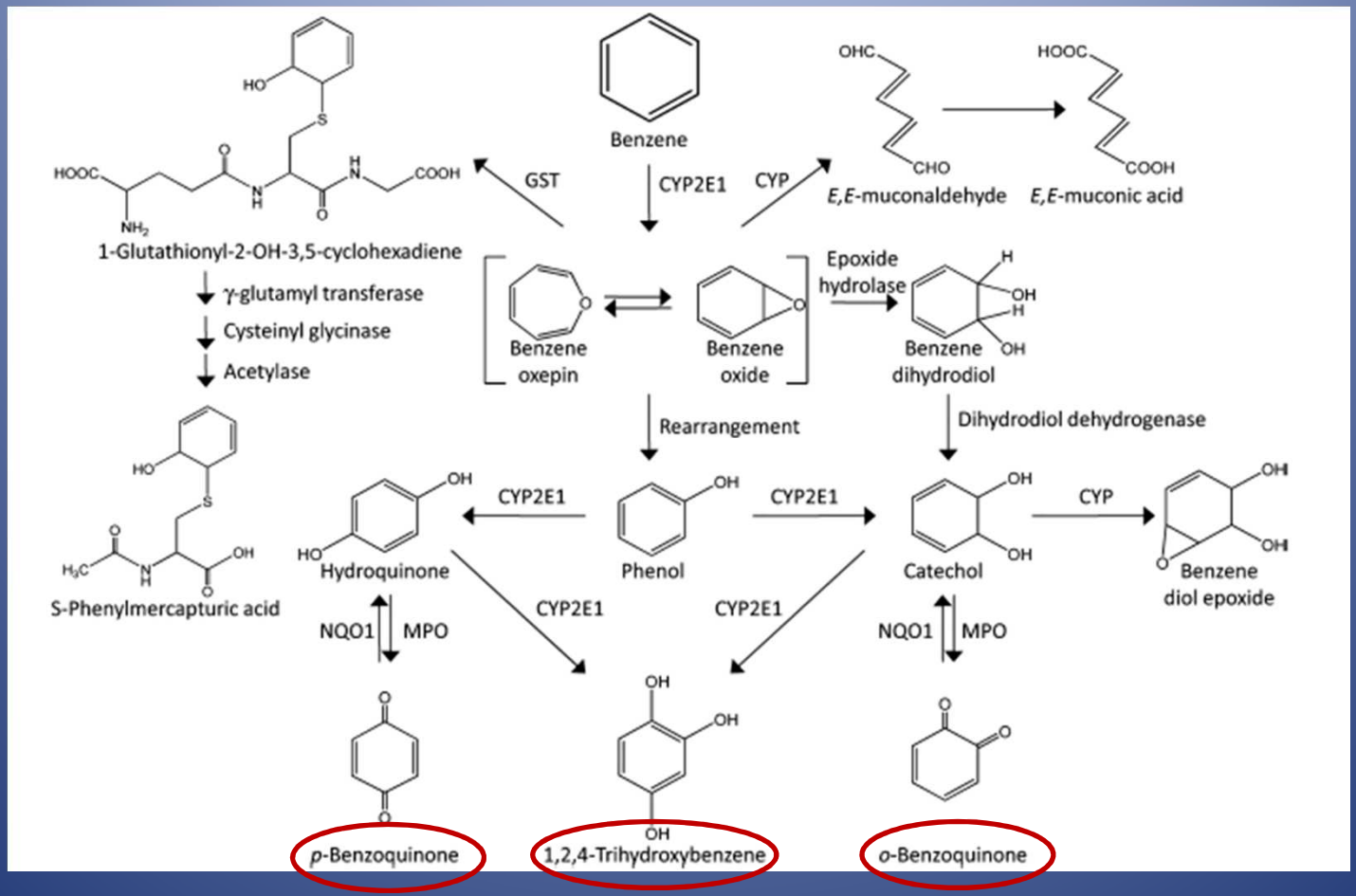
Benzene

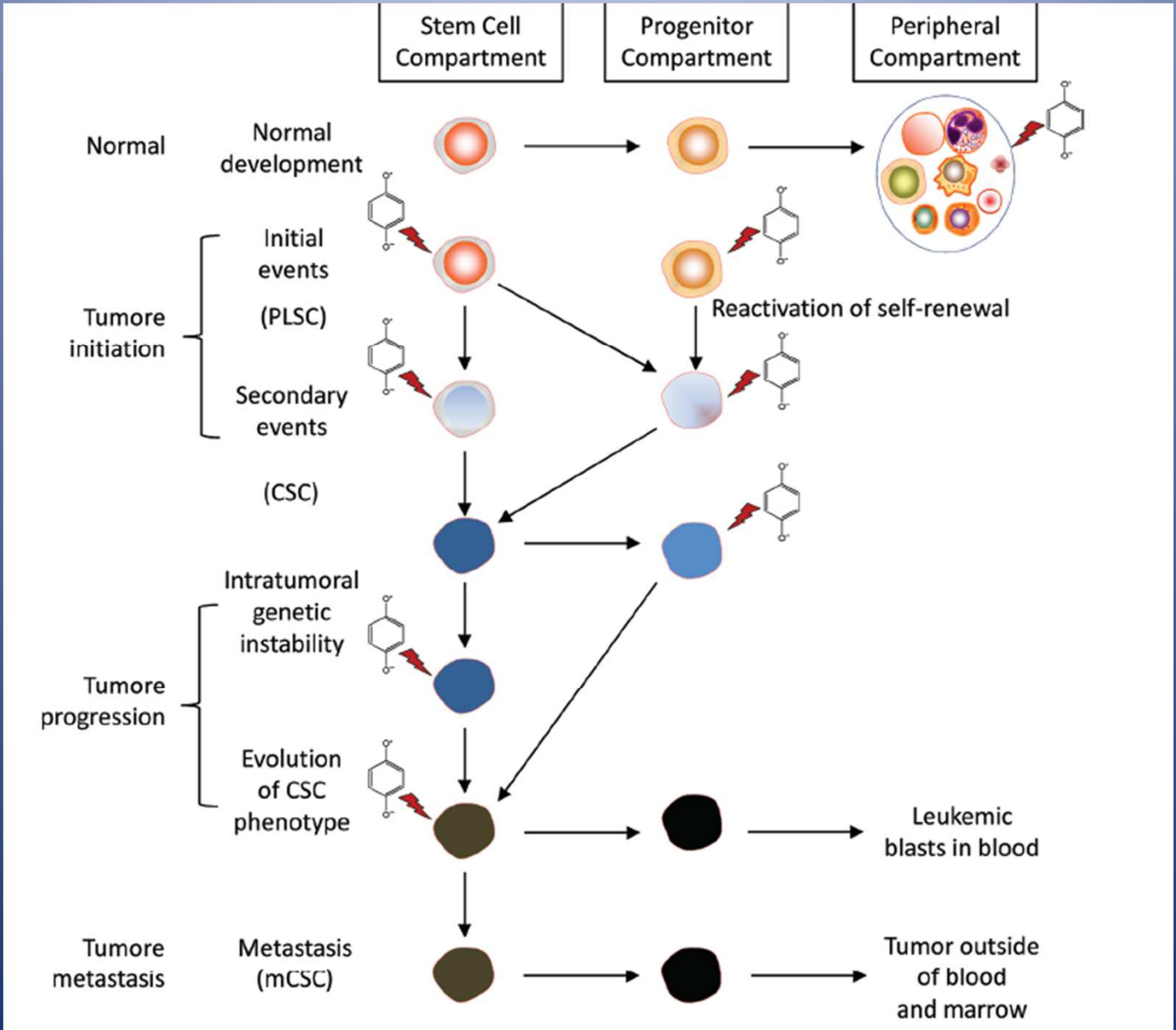

Benzene
GST
CYP2E1
CYP
E,E-muconaldehyde
E,E-muconic acid
1-Glutathionyl-2-OH-3,5-cyclohexadiene
γ-glutamyl transferase
Cysteinyl glycinase
Acetylase
Benzene oxepin
Benzene oxide
Epoxide hydrolase
Benzene dihydrodiol
Rearrangement
Dihydrodiol dehydrogenase
S-Phenylmercapturic acid
Hydroquinone
Phenol
Catechol
Benzene diol epoxide
NQO1
MPO
p-Benzoquinone
1,2,4-Trihydroxybenzene
o-Benzoquinone

MODE OF ACTION (MOA) of benzene:

benzene metabolites formed through metabolism in the liver and bone marrow cause damage in hematopoietic cells via multiple mechanisms, mainly chromosomal aberrations and DNA repair functions damage:
:

1) Oxidative stress
2) Chronic exposure to benzene is associated with high levels of chromosomal changes including 5q −/−5 or 7q−/−7, +8, and t(8:21) in peripheral blood cell.
3) Benzene could cause leukemias with chromosomal translocations and inversions known to be induced by topo II inhibition, such as t(21q22), t(15;17), and inv(16).
4) DNA adducts from benzene have been postulated, including N7-phenylguanine and 3′-OH-1,N2-benzetheno-2′deoxyguanosine.
5) P53 is mutated

McHale et al. 2012, Carcinogenesis
Wang et al 2012, Chemical research in toxicology

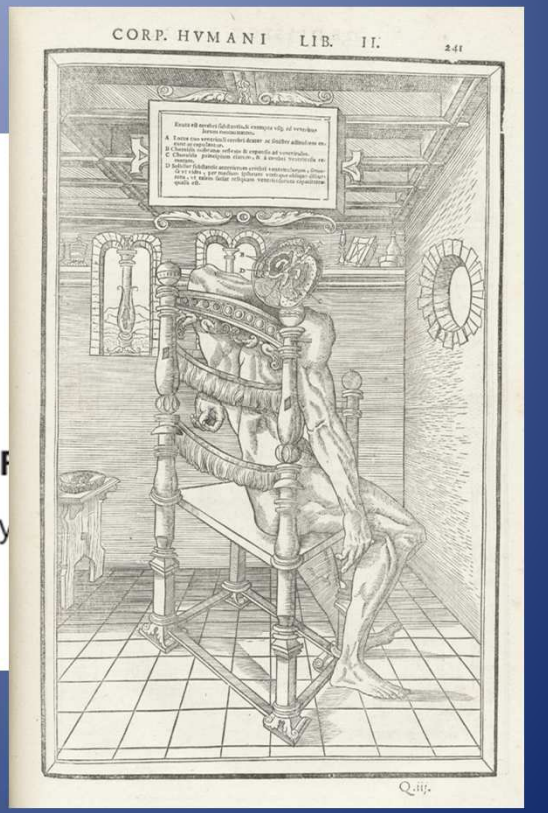

Stem Cell Compartment
Progenitor Compartment
Peripheral Compartment
Normal
Normal development
Tumore initiation
Initial events
(PLSC)
Secondary events
(CSC)
Reactivation of self-renewal
Tumore progression
Intratumoral genetic instability
Evolution of CSC phenotype
Leukemic blasts in blood
Tumore metastasis
Metastasis (mCSC)
Tumor outside of blood and marrow

Effects of Benzene and Its Metabolites on Global DNA Methylation in Human Normal Hepatic L02 Cells

Junjie Hu,[1,2] Huimin Ma,[1] Wenbing Zhang,[1] Zhiqing Yu,[1] Guoying Sheng,[1] Jiamo F

[1]State Key Laboratory of Organic Geochemistry, Guangzhou Institute of Geochemistry Chinese Academy of Sciences, Guangzhou 510640, China

[2]Graduate School of the Chinese Academy of Science, Beijing, China



Asbesto

Tumor and Stem Cell Biology

Cancer Research

Tumor Suppressor Alterations Cooperate to Drive Aggressive Mesotheliomas with Enriched Cancer Stem Cells via a p53–miR-34a–c-Met Axis

Craig W. Menges[1], Yuwaraj Kadariya[1], Deborah Altomare[2], Jacqueline Talarchek[1], Erin Neumann-Domer[1], Yue Wu[1,4], Guang-Hui Xiao[4], Irina M. Shapiro[3], Vihren N. Kolev[3], Jonathan A. Pachter[3], Andres J. Klein-Szanto[1], and Joseph R. Testa[1]

Wood dust

The general idea is that wood dust generates Inflammation and therefore triggers oxidative stress and free radical production and may indirectly result in genotoxic effects (Kundu and Surh, 2008). Several different wood types have been evaluated for proinflammatory effects using immortalized cell lines or rodents as models. Induction of inflammatory responses by wood dusts or extracts resulted in expression of specific chemokines, cytokines, and proinflammatory enzymes.

Environmental Toxicology DOI 10.1002/tox

Activation of Aryl Hydrocarbon Receptor Signaling by Extracts of Teak and Other Wood Dusts

Mark J. Wilson, Gabriele Sabbioni, Roy Rando, Charles A. Miller III

Department of Global Environmental Health Sciences, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana 70112

2-methylanthraquinone (2-MAQ) accounted for the AhR ligand activity

Smoking is associated with mosaic loss of chromosome Y

Jan P. Dumanski,[1,2]* Chiara Rasi,[1,2] Mikael Lönn,[3] Hanna Davies,[1,2] Martin Ingelsson,[4] Vilmantas Giedraitis,[4] Lars Lannfelt,[4] Patrik K. E. Magnusson,[5] Cecilia M. Lindgren,[6,7] Andrew P. Morris,[6,8] David Cesarini,[9] Magnus Johannesson,[10] Eva Tiensuu Janson,[11] Lars Lind,[11] Nancy L. Pedersen,[5] Erik Ingelsson,[2,11] Lars A. Forsberg[1,2]*

Tobacco smoking is a risk factor for numerous disorders, including cancers affecting organs outside the respiratory tract. Epidemiological data suggest that smoking is a greater risk factor for these cancers in males compared with females. This observation, together with the fact that males have a higher incidence of and mortality from most non–sex-specific cancers, remains unexplained. Loss of chromosome Y (LOY) in blood cells is associated with increased risk of nonhematological tumors. We demonstrate here that smoking is associated with LOY in blood cells in three independent cohorts [TwinGene: odds ratio (OR) = 4.3, 95% confidence interval (CI) = 2.8 to 6.7; Uppsala Longitudinal Study of Adult Men: OR = 2.4, 95% CI = 1.6 to 3.6; and Prospective Investigation of the Vasculature in Uppsala Seniors: OR = 3.5, 95% CI = 1.4 to 8.4] encompassing a total of 6014 men. The data also suggest that smoking has a transient and dose-dependent mutagenic effect on LOY status. The finding that smoking induces LOY thus links a preventable risk factor with the most common acquired human mutation.

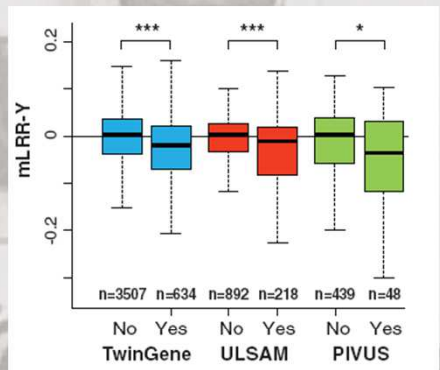
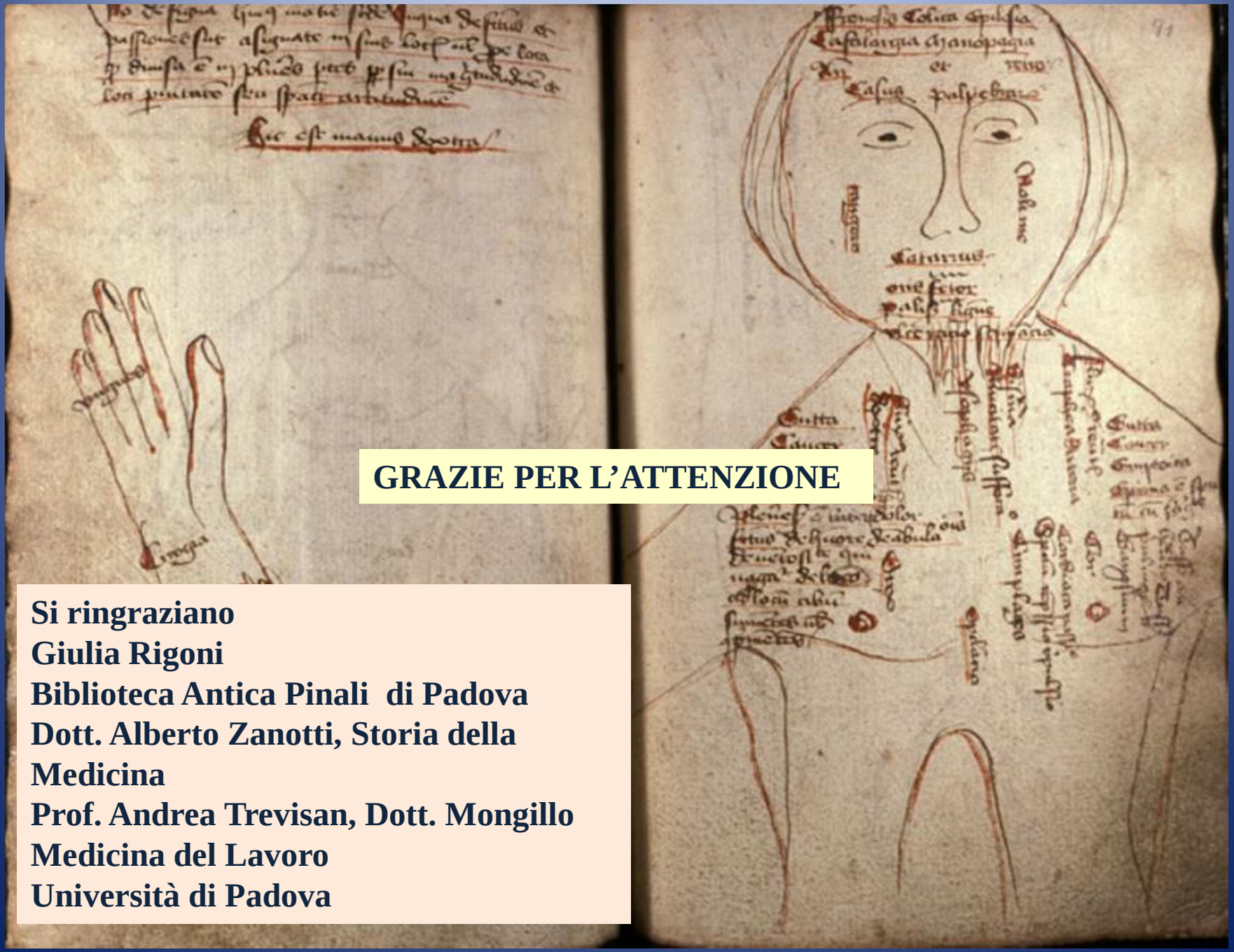


Fig. 1. The association between smoking status and the level of LOY (i.e., mLRR-Y) in three independent cohorts. In all cohorts, these unadjusted analyses indicate that the current smokers (Yes) (table S5) had a significantly higher degree of mosaic LOY in blood, compared with noncurrent smokers (No), composed of never-smokers and previous smokers. ***$P < 0.001$; *$P < 0.05$ (Kolmogorov-Smirnov tests: TwinGene, $D = 0.15$, $P = 1.131 \times 10^{-11}$; ULSAM, $D = 0.15$, $P = 0.0006$; PIVUS, $D = 0.23$, $P = 0.0203$). The definitions used for LOY scoring and the entire ranges of mLRR-Y data observed in each cohort are shown in figs. S3 to S5.



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