CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2015-2016 :
"Epigénétique et Cancer"

7 mars, 2016

Cours II
"La génomique et l'épigénomique des cancers et leur apport à la compréhension des mécanismes"

"*Cancer Genomes and Epigenomics: from maps to mechanisms*"

E. Heard, 2016

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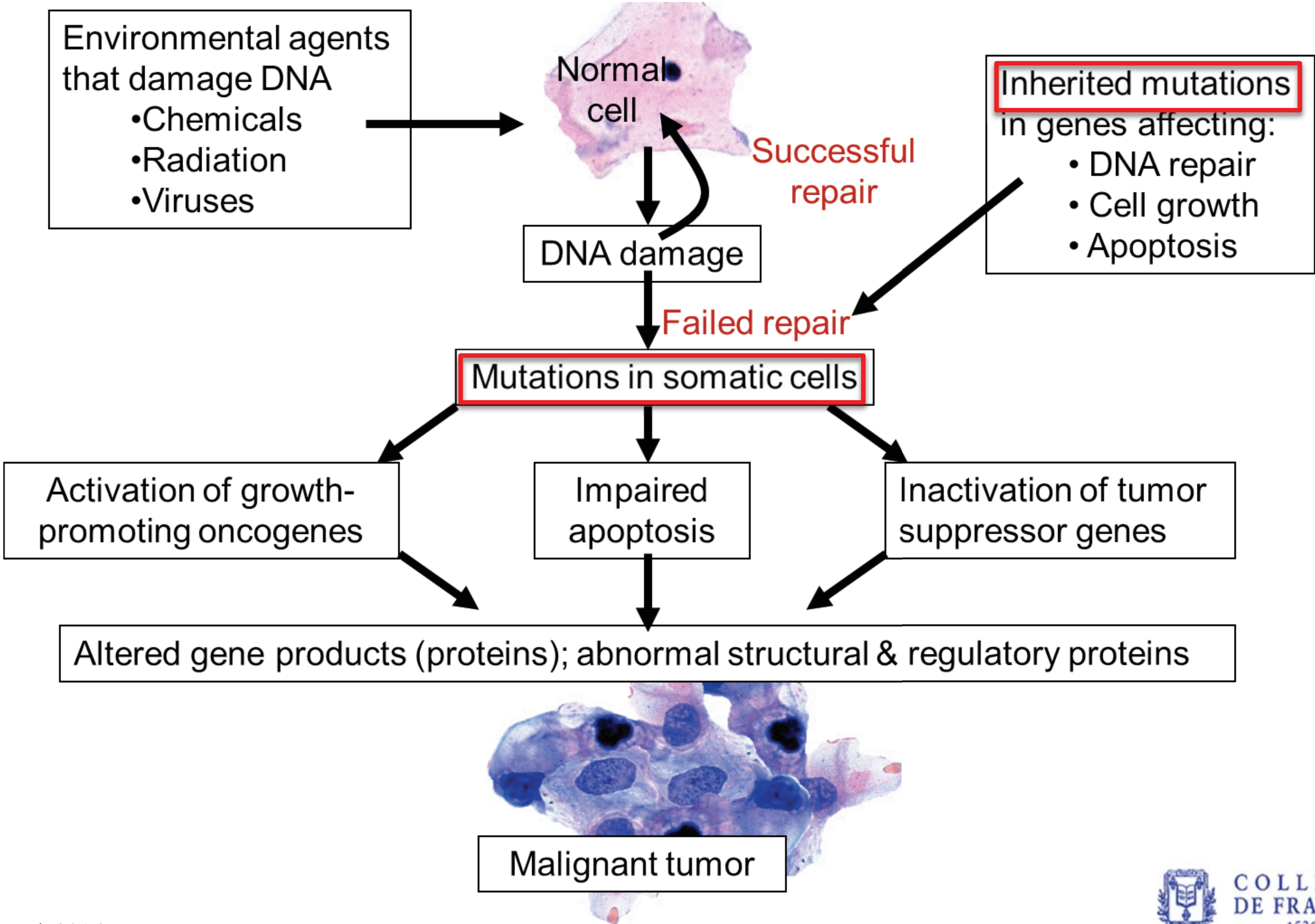
Overview of Carcinogenesis



E. Heard, 2016

Prevailing View of Carcinogenesis

(B. Vogelstein and others)

• Cancer is a genetic disease. It is caused by an accumulation of mutations in genes that control the birth, growth, and death of the body's cells.

• A cell must acquire multiple mutations before it becomes cancerous. It can take decades for cells to amass these changes.

• Some genetic 'errors' are inherited, ie person is born with an increased susceptibility to cancer because their cells have a mutational "head start" down the pathway to disease. Families in which individuals are prone to develop a specific cancer have helped researchers identify the responsible genes (tumor suppressors in particular).

• The majority of cancer-related mutations occur after birth, triggered, for example, by environmental factors, such as sunlight or cigarette smoke.

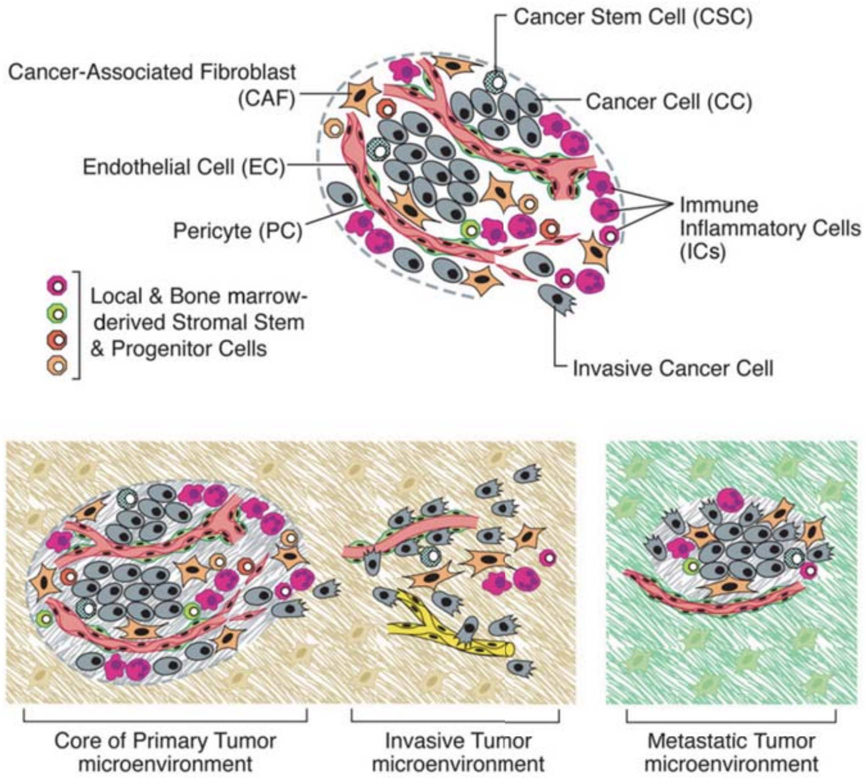
• Alternatively, cancer-related somatic mutations are simply a result of "errors" depending on the number of "stem" cell divisions (see Vogelstein, 2015)

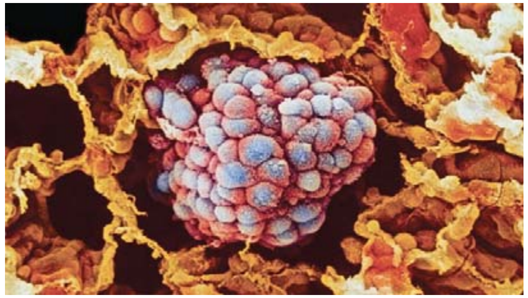
• A tumor is a mass of cells that forms when a single cell acquires a mutation that gives it a slight growth advantage over its neighbors. A tumor is considered cancerous when its cells begin to invade surrounding tissue. Some of these cells may break free and establish additional tumors throughout the body, where they can damage vital organs.

• Genes involved in cancer fall into three broad categories: genes that normally keep cell division in check; genes that promote cell proliferation; and genes that repair damaged DNA. Mutations in any of these processes can lead to cancer (Review by Vogelstein et al, 2013).

But….

Prevailing View of Carcinogenesis





Lung carcinoma (blue) filling an alveolus of the human lung

Cancer is a complex condition

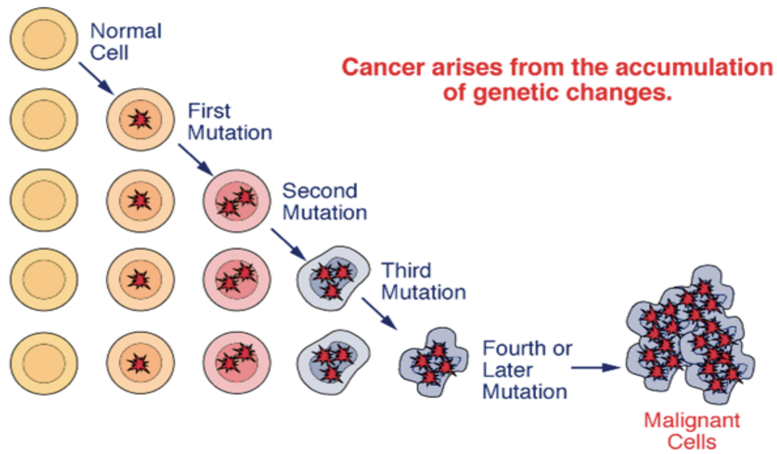
Tumors are dynamic "ecosystems", with evolving genotypes/phenotypes
And interactions between different cancer cells, the stroma,
the immune system, even bacteria…

Cancer cells seems to have inherent plasticity and evolvability?

Hanahan and Weinberg, Cell 2011

Somatic Mutation Model for Cancer

The prevailing model for cancer development was that **mutations** in genes for tumor suppressors and oncogenes lead to cancer.



"Each tumor seemed a unique experiment of nature – acquiring a unique set of mutant genes in an unpredictable chronological order…"
(R. Weinberg, Cell 2014)

Was this view too simple?

- Different cancers seem to involve very different sets of genes (except for specific hematological cancers)
- Rates of somatic mutation ($\underset{\sim}{\sim}10^{-8}$) do not easily explain the rapid evolution of many tumors – (except where DNA repair genes are mutated)
- Model does not explain the many chromosomal aberrations typical of cancer cells
- Fails to explain the genetic diversity among cells within a single tumor
- Does not easily explain frequent resistance to therapies

Epigenetic models – Epimutations and/or global epigenetic changes based on DNA Methylation (proposed by R. Holliday in the 1970's, later by R. Feinberg, S.Baylin, P. Jones, S. Clark & others)
As well as chromatin proteins (eg Polycomb, Trithorax) - & non-coding RNAs (Cours 2015)

DNA Methylation is a classic "epigenetic" mark that may have several roles in cancer

generating both *epi*mutations and mutations

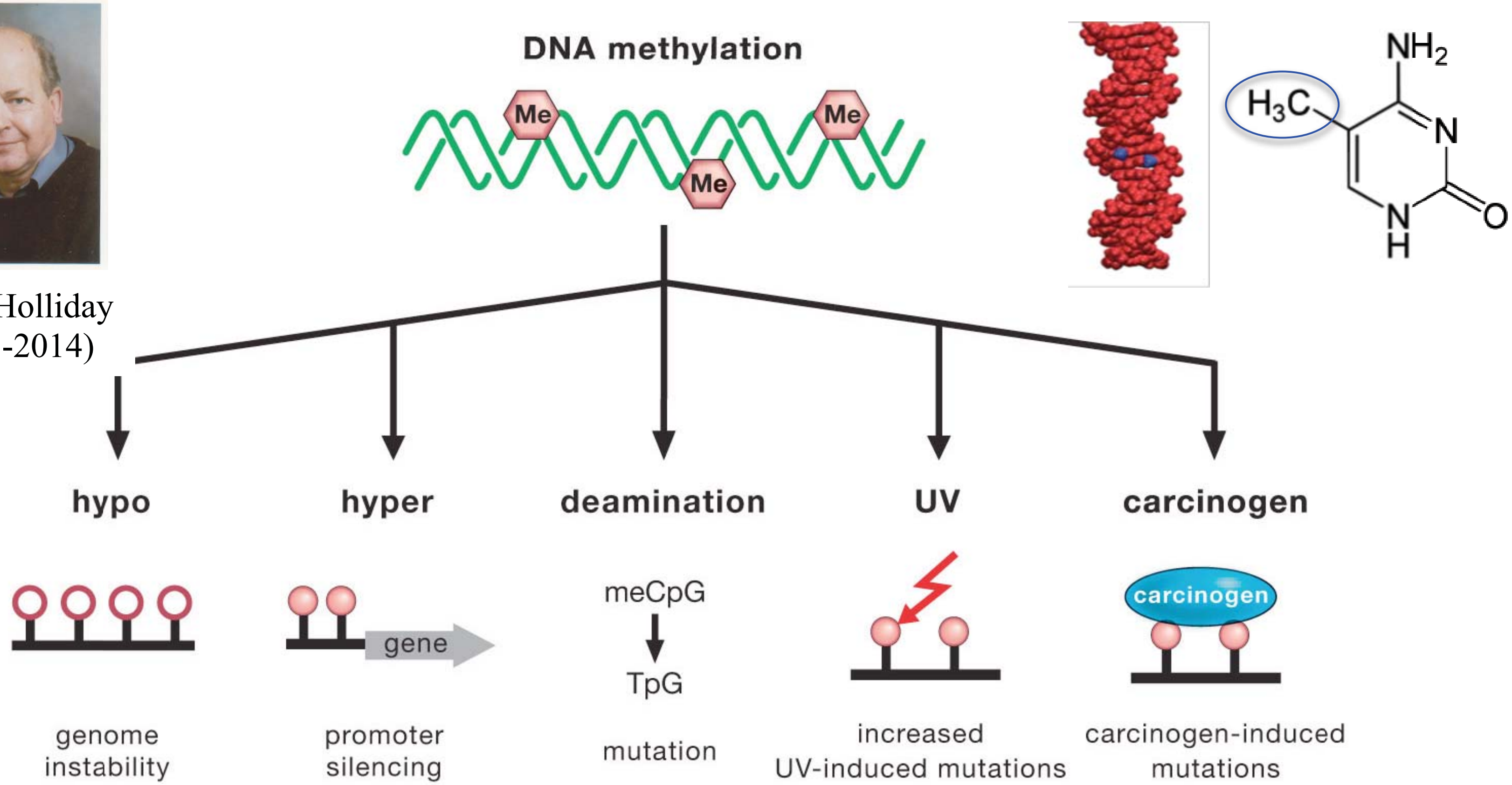
Br. J. Cancer (1979) **40**, 513

A NEW THEORY OF CARCINOGENESIS*

R. HOLLIDAY

Robin Holliday
(1935-2014)

The "5th base"



More NEXT WEEK (COURS III)

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Définition de l'épigénétique (Holliday – Riggs)

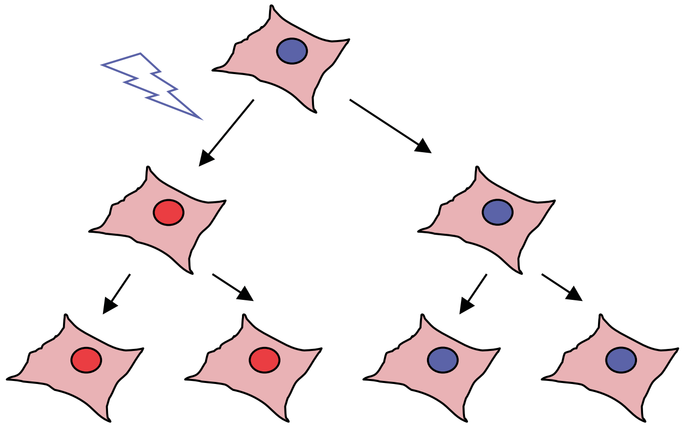
L'étude des changements d'expression des gènes transmissibles au travers des divisions cellulaires (voire des générations), sans changement de la séquence de l'ADN

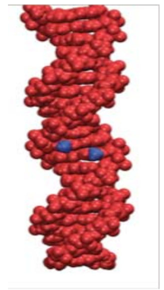
Epigénétique et Mémoire Cellulaire

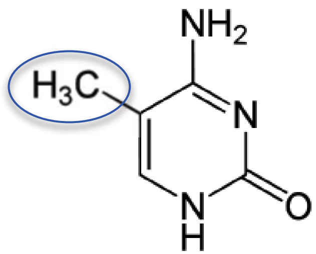
Russo, V.E.A., R.A. Martienssen & A.D. Riggs Eds. 1996.
Cold Spring Harbor Laboratory Press.

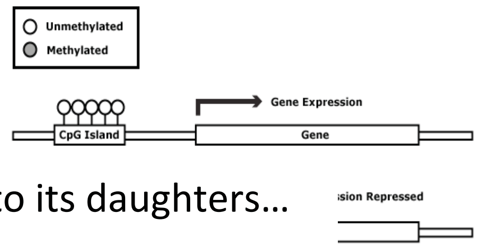
Robin Holliday
(1935-2014)

Art Riggs
(born 1939)

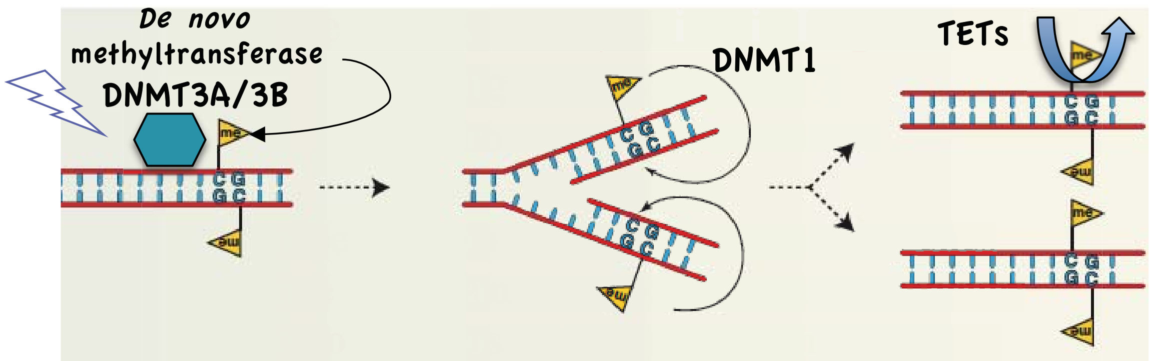


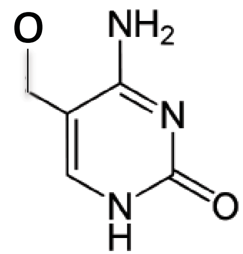






Faithful transmission of DNA methylation patterns from one cell to its daughters…
May be less faithful than DNA sequence replication …





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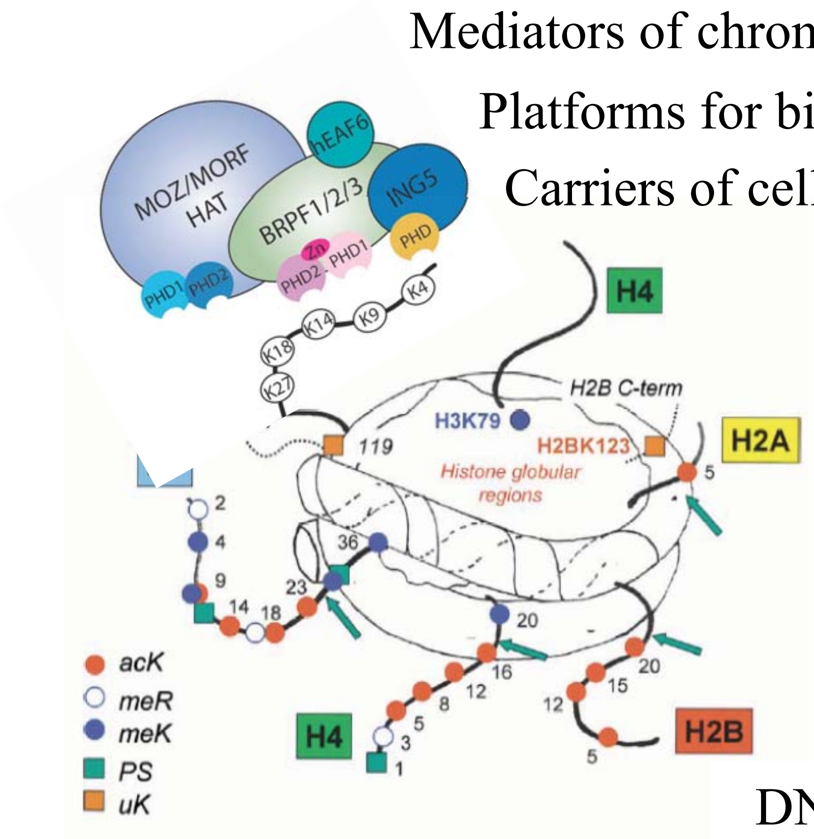
Chromatin-based States and Partners

Histone Variants and Histone Modifications are:

Mediators of chromatin accessibility

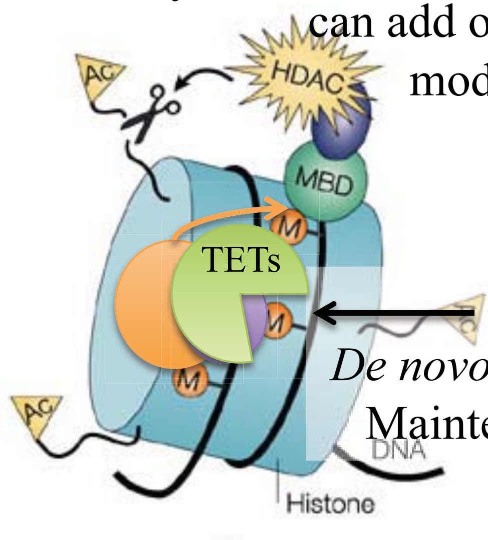
Platforms for binding proteins

Carriers of cellular memory



Cell (2002): 285-291

Histone modifying enzymes can add or remove these modifications



Dnmts

De novo: Dnmt3a,3b, 3L

Maintenance: Dnmt1

DNA methylation associated with repressed state of some genes, repeats:

Self-templating, stable - but can be removed (**actively** eg Tet-induced conversion to 5hme; **passively** during DNA replication)

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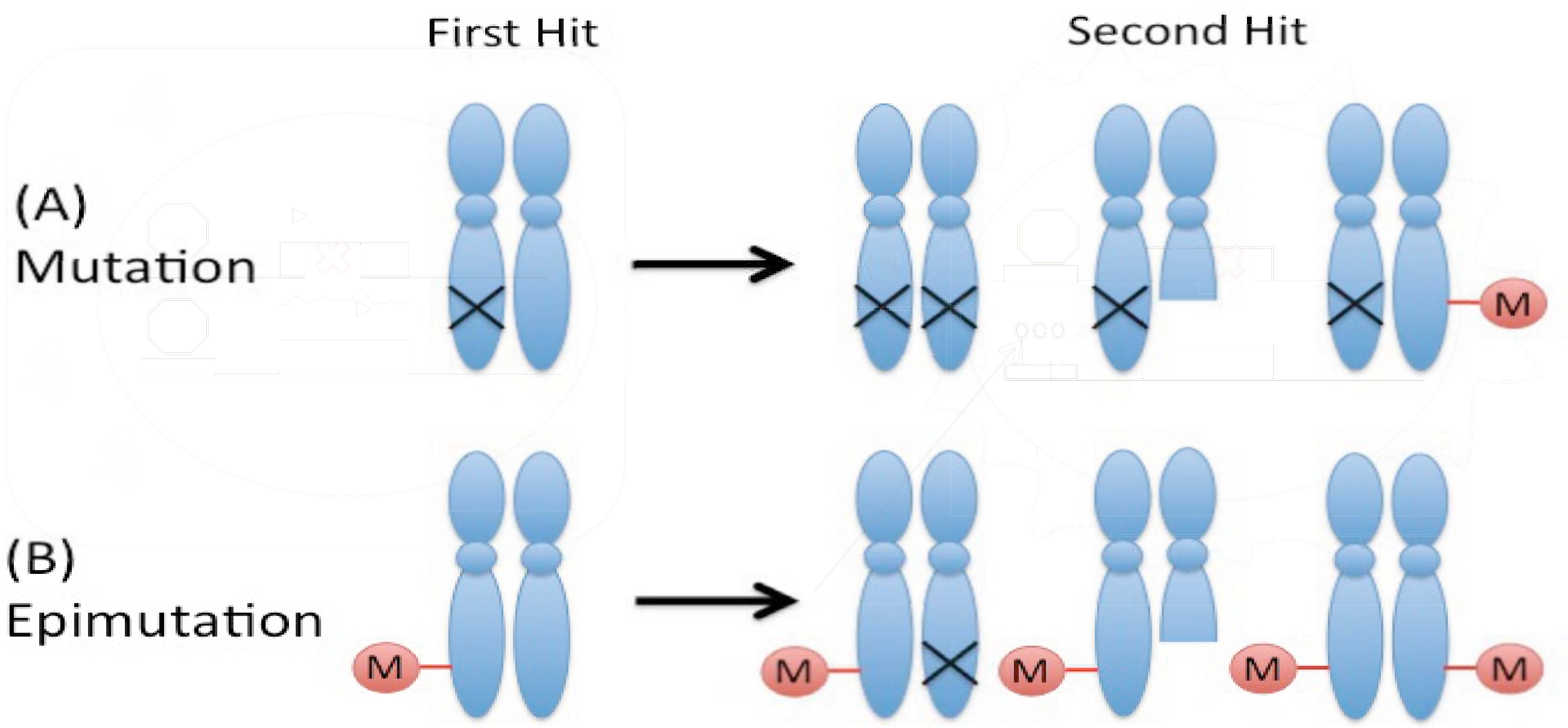
Epigenetic Models for Cancer

Evidence for DNA methylation changes in cancer

(pre-genome wide technologies)

- **Global DNA hypomethylation** in cancer cell lines (Dilala and Hoffman, 1982; Ehrlich, 1982)
- **Local DNA hypomethylation at some oncogenes** – eg *Ras* (Feinberg and Vogelstein, 1983)
- **DNA hypermethylation of CpG islands of multiple tumor suppressor genes** (reviewed by Jones and Baylin, 2002)



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Numerous examples of Promoter CpG island Hypermethylation of Tumor Suppressor genes in cancer

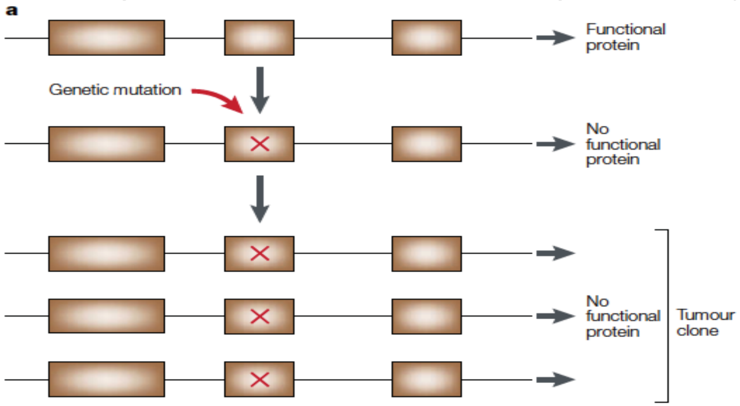
Table 1 Selected genes that undergo CpG island hypermethylation in human cancer

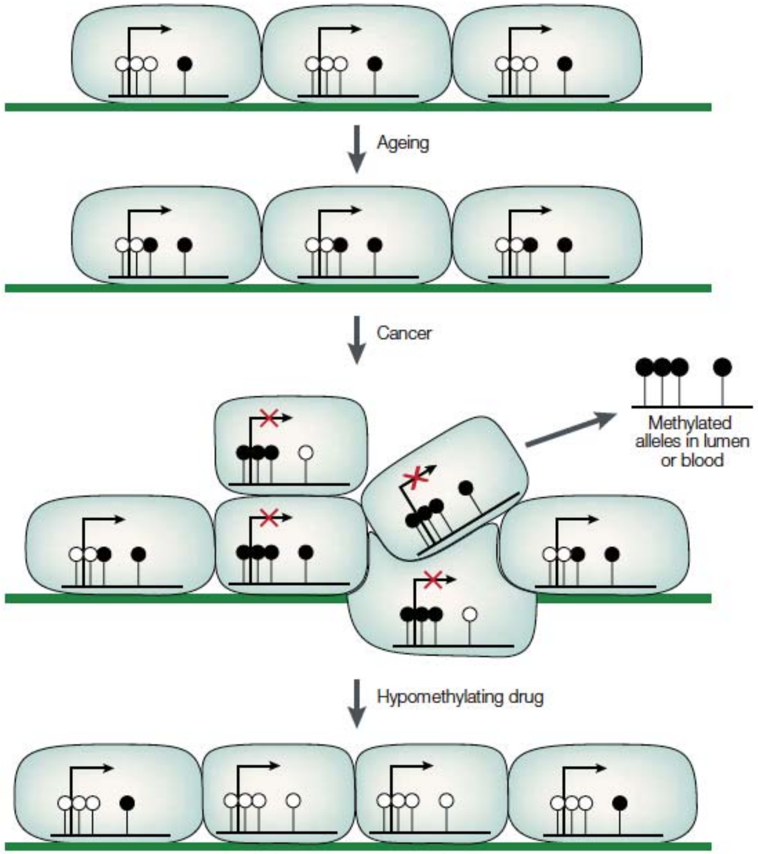
Gene	*Function*	*Location*	*Tumor profile*	*Consequences*
p16^{INK4a}	Cyclin-dependent Kinase Inhibitor	9p21	Multiple Types	Entrance in Cell Cycle
p14^{ARF}	*MDM2* inhibitor	9p21	Colon, Stomach, Kidney	Degradation of *p53*
p15^{INK4b}	Cyclin-dependent Kinase Inhibitor	9p21	Leukemia	Entrance in Cell Cycle
hMLH1	DNA mismatch repair	3p21.3	Colon, Endometrium, Stomach	Frameshift Mutations
MGMT	DNA repair of 06-alkyl-guanine	10q26	Multiple Types	Mutations, Chemosensitivity
GSTP1	Conjugation to Glutathione	11q13	Prostate, Breast, Kidney	Adduct Accumulation?
BRCA1	DNA Repair, Transcription	17q21	Breast, Ovary	Double Strand-Breaks?
p73	p53 Homologue	1p36	Lymphoma	Unknown (Cisplatin?)
LKB1/STK11	Serine/Threonine Kinase	19p13.3	Colon, Breast, Lung	Unknown
ER	Estrogen Receptor	6q25.1	Breast	Hormone Insensitivity
PR	Progesterone Receptor	11q22	Breast	Hormone Insensitivity
AR	Androgen Receptor	Xq11	Prostate	Hormone Insensitivity
RARβ2	Retinoic Acid Receptor β2	3p24	Colon, Lung, Head and Neck	Vitamin Insensitivity?
RASSF1	Ras Effector Homologue	3p21.3	Multiple Types	Unknown
VHL	Ubiquitin Ligase Component	3p25	Kidney, Hemangioblastoma	Loss of hypoxic response?
Rb	Cell Cycle Inhibitor	13q14	Retinoblastoma	Entrance in Cell Cycle
THBS-1	Thrombospondin-1, Anti-angiogenic	15q15	Glioma	Neovascularization
CDH1	E-cadherin, cell adhesion	16q22.1	Breast, Stomach, Leukemia	Dissemination
HIC-1	Transcription Factor	17p13.3	Multiple Types	Unknown
APC	Inhibitor of β-catenin	5q21	Aerodigestive Tract	Activation β-catenin Route
COX-2	Cyclooxigenase-2	1q25	Colon, Stomach	Antinflamatory Resistance?
SOCS-1	Inhibitor of JAK/STAT Pathway	16p13.13	Liver	JAK2 Activation
SRBC	*BRCA1*-binding Protein	1p15	Breast, Lung	Unknown
SYK	Tyrosine Kinase	9q22	Breast	Unknown
RIZ1	Histone/Protein Methyltransferase	1p36	Breast, Liver	Aberrant Gene Expression?
CDH13	H-cadherin, cell adhesion	16q24	Breast, Lung	Dissemination?
DAPK	Pro-apoptotic	9q34.1	Lymphoma, Lung, Colon	Resistance to Apoptosis
TMS1	Pro-apoptotic	16p11	Breast	Resistance to Apoptosis
TPEF/HPP1	Transmembrane Protein	2q33	Colon, Bladder	Unknown

Source: CpG island hypermethylation in cancer
M Esteller, Oncogene 2002

The Attraction of Epigenetic Models for Cancer

- Dosage may be a key consideration for some proteins' selective advantage in cancer:
  Most genetic changes lead to an all-or-nothing gene expression change
  Epigenetic changes can lead to *range of expression levels – & can be stable in this range*
- Epigenetic changes can arise stochastically & be metastable: can explain tumor *heterogeneity*?
- Epigenetic changes can be reversed (eg 5-Aza-cytidine): therapeutic potential





From Jones and Baylin, 2002

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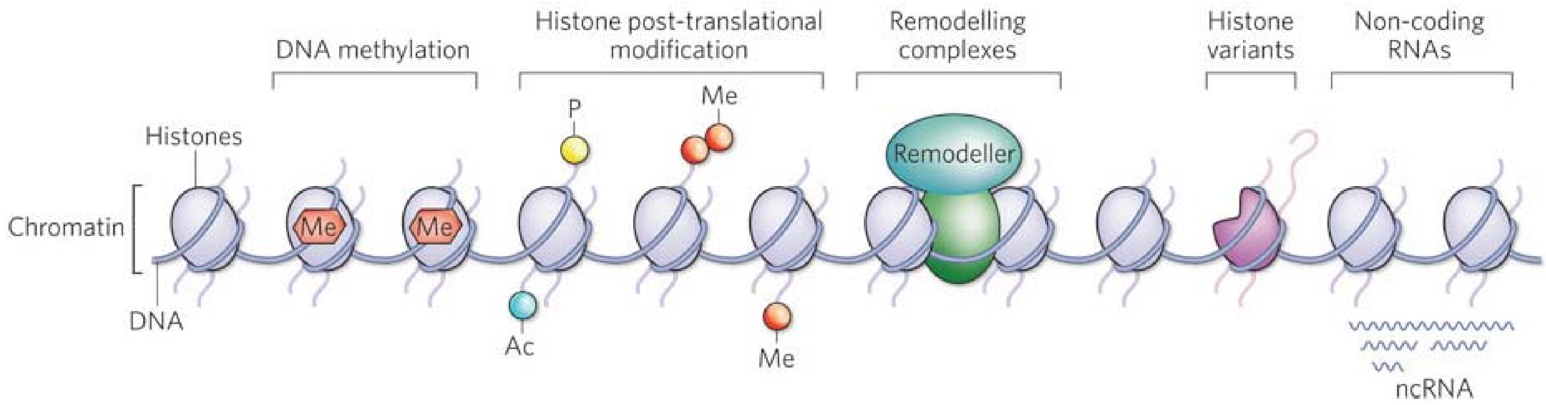
Epigenetic Models for Cancer

- Both genetic and epigenetic views ultimately involve ***abnormal gene expression***.
- The expression state of a gene is determined by presence of TFs, chromatin remodelers and modifying enzymes, and the packaging of its DNA regulatory landscape.
- DNA mutations of tumor suppressors and/or oncogenes cause either loss or gain of function and abnormal expression.
- Do epigenetic pathways actually matter in cancer? Factors affecting chromatin structure, DNA me, histone variants and modifications, nucleosome remodeling…



Epigenetic Models for Cancer

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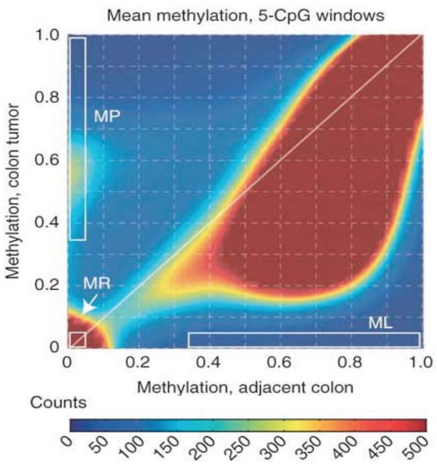
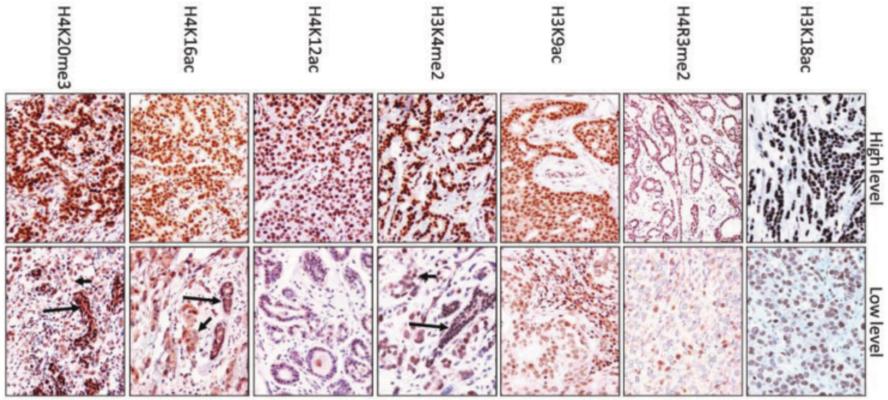
- Do epigenetic pathways actually matter in cancer? Factors affecting chromatin structure, DNA me, histone variants and modifications, nucleosome remodeling…
- Frequent global loss of 5mC, some cancers show a *CpG island methylator phenotype* (CIMP) (Toyota et al., 1999), global changes in chromatin structure/state (by IHC, IF)

What are the <u>genome-wide distributions</u> of DNA methylation, nucleosome occupancy, chromatin state profiles?

Berman *et al., Nat Genet. 2011*





Global Histone Modifications in Breast Cancer Correlate with Tumor Phenotypes, Prognostic Factors, and Patient Outcome. Elsheikh *Cancer Res* 2009

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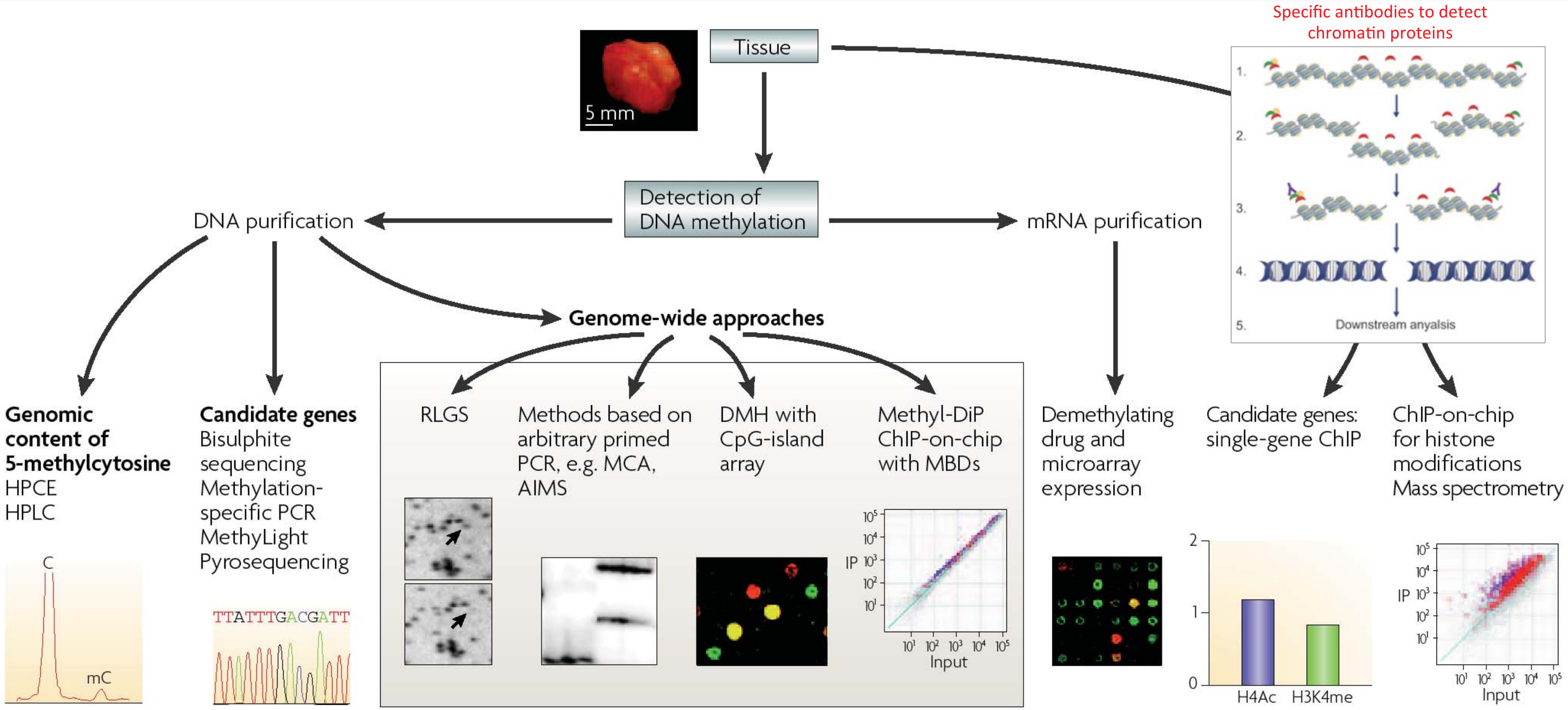
Epigenomic Mapping in Cancer



Esteller, NRG, 2007

>28 million CpG sites in the human genome. Assessing the methylation status of each of these sites will be required to understand fully the role of DNA methylation in health and disease. Except for whole-genome bisulfite sequencing (WGBS), most commonly used genome-wide methods detect <5% of all CpG sites. WGBS studies are >> costly, require specialised expertise and bioinformatics…

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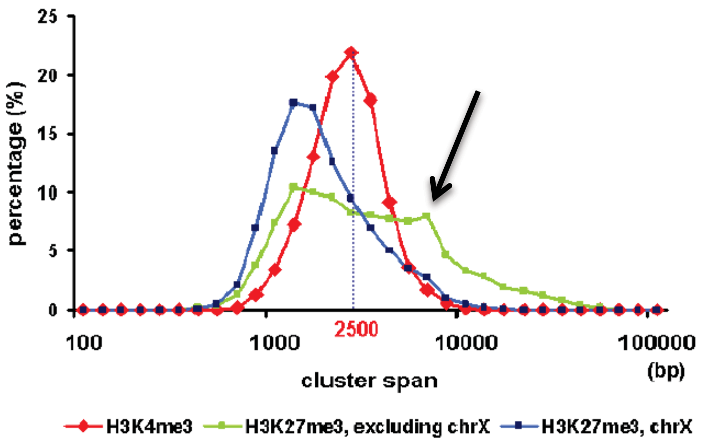
Organisation of the genome into large organised chromatin blocks

Large blocks of “silent” chromatin, spanning several hundreds of kilobases often associated with nuclear lamina (LADs) exist in normal mammalian cells

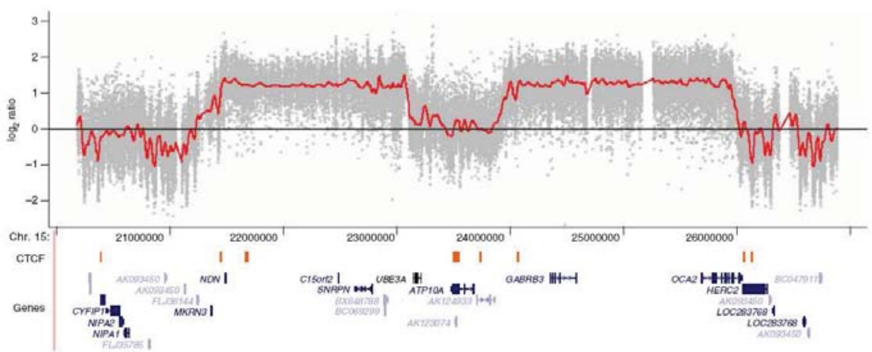
<u>Autosomal H3K27me3 domains</u>



mES cells

Zhao *et al.*, 2007

<u>Autosomal H3K9me2 domains</u>



LOCKs (large organised chromatin K9 modifications)
chr15 in placenta cells

Wen *et al.*, 2009

BLOCs (broad local regions of enrichment) in MEF cells

Pauler *et al.*, 2007

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Courtesy of C. Vallot

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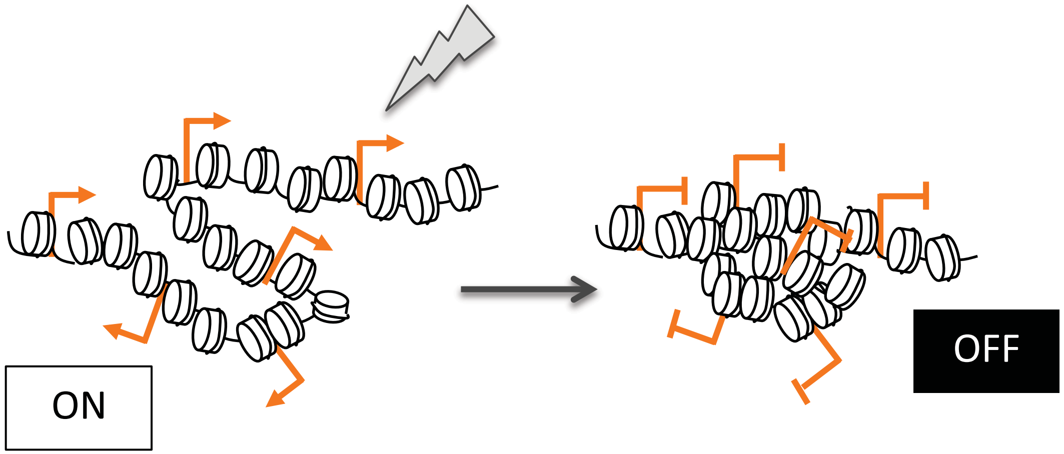
Disruption of genome organization occurs in cancer

Regions corresponding to these blocks, spanning several hundreds of kilobases, show coordinated aberrant repression or activation in cancer

Long-Range Epigenetic Silencing (**LRES**) alterations



Integration of micro-array and CGH data to create correlation maps and gene signatures

Long-Range Epigenetic Silencing (**LREA**) alterations

BLADDER CANCER
Stransky and Vallot *et al.*, Nat Genet 2006

COLON CANCER
Frigola *et al.*, 2006

BREAST CANCER
Novak *et al.*, 2006

PROSTATE CANCER
Coolen *et al.*, 2010

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Courtesy of C. Vallot

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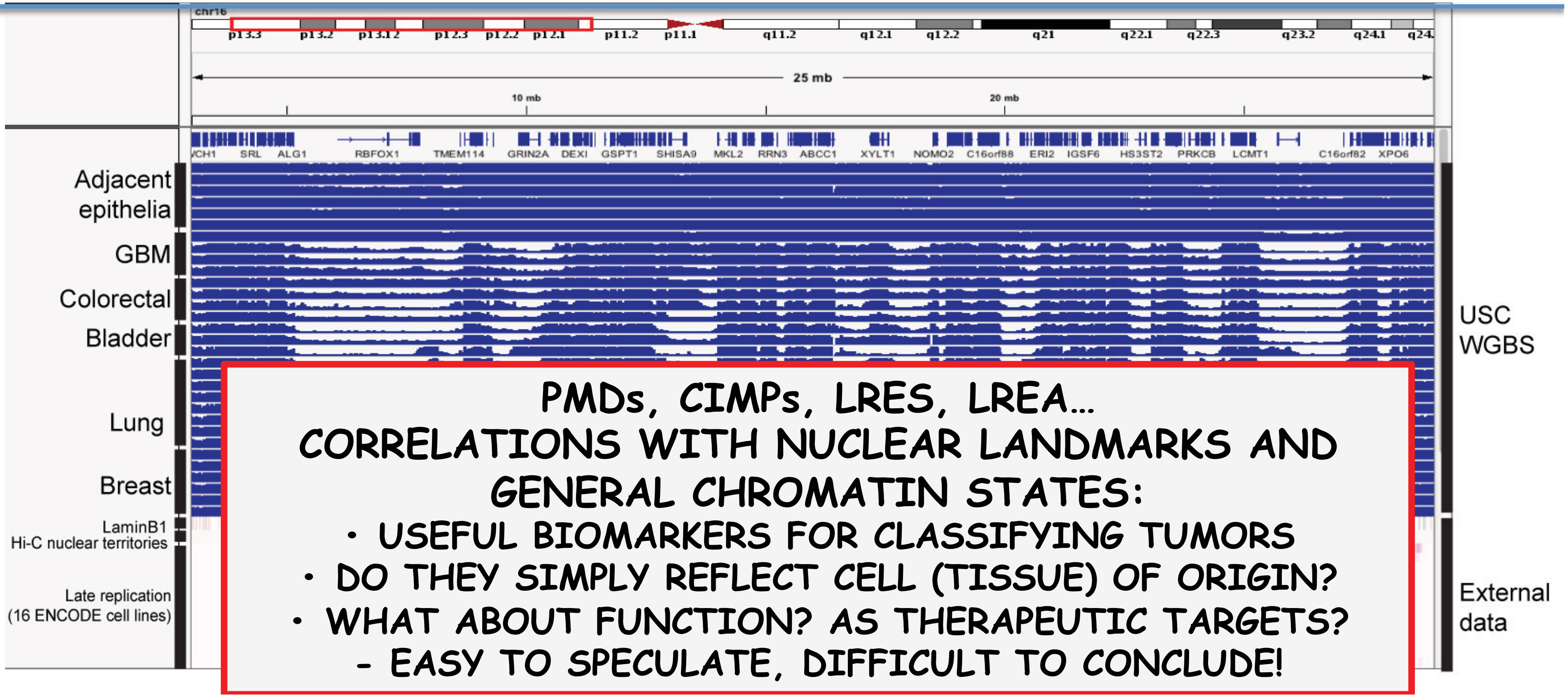
Partially Methylated Domains (PMDs) are pervasive in cancer



PMDs, CIMPs, LRES, LREA…
CORRELATIONS WITH NUCLEAR LANDMARKS AND GENERAL CHROMATIN STATES:

- **USEFUL BIOMARKERS FOR CLASSIFYING TUMORS**
- **DO THEY SIMPLY REFLECT CELL (TISSUE) OF ORIGIN?**
- **WHAT ABOUT FUNCTION? AS THERAPEUTIC TARGETS?**

- EASY TO SPECULATE, DIFFICULT TO CONCLUDE!

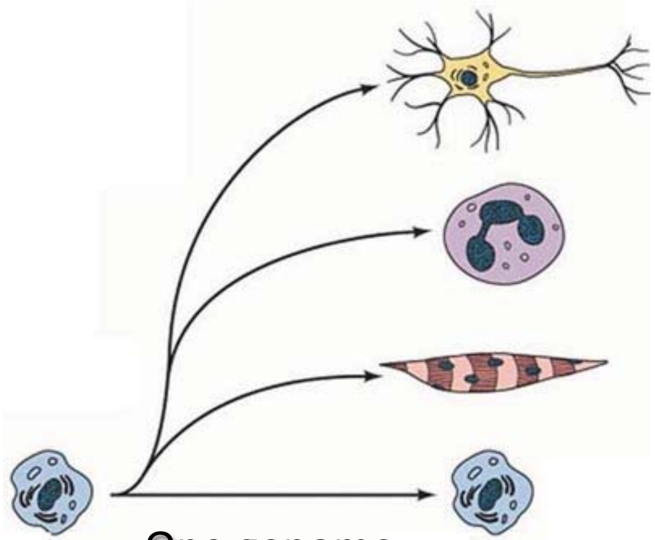
Sproul et al, 2014 “Transcriptionally repressed genes become aberrantly methylated and distinguish tumors of different lineages in breast cancer” doi: 10.1073/pnas.1013224108

Holm et al, 2016 “An integrated genomics analysis of epigenetic subtypes in human breast tumors links DNA methylation patterns to chromatin states in normal mammary cells”. Breast Cancer Res. 2016;18(1):27

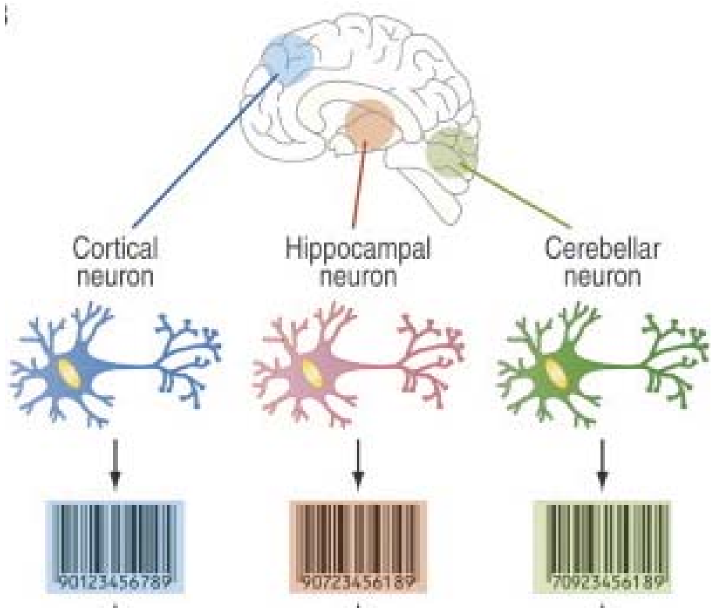
“Our results suggest that hypermethylation patterns across basal-like breast cancer may have limited influence on tumor progression and instead reflect the repressed chromatin state of the tissue of origin. On the contrary, hypermethylation patterns specific to luminal breast cancer influence gene expression, may contribute to tumor progression, and may present an actionable epigenetic alteration in a subset of luminal breast cancers.”

E.

How to Interpret Cancer Epigenomes?



One genome
Multiple Epigenomes



Cancer: multiple "genomes" and "epigenomes"

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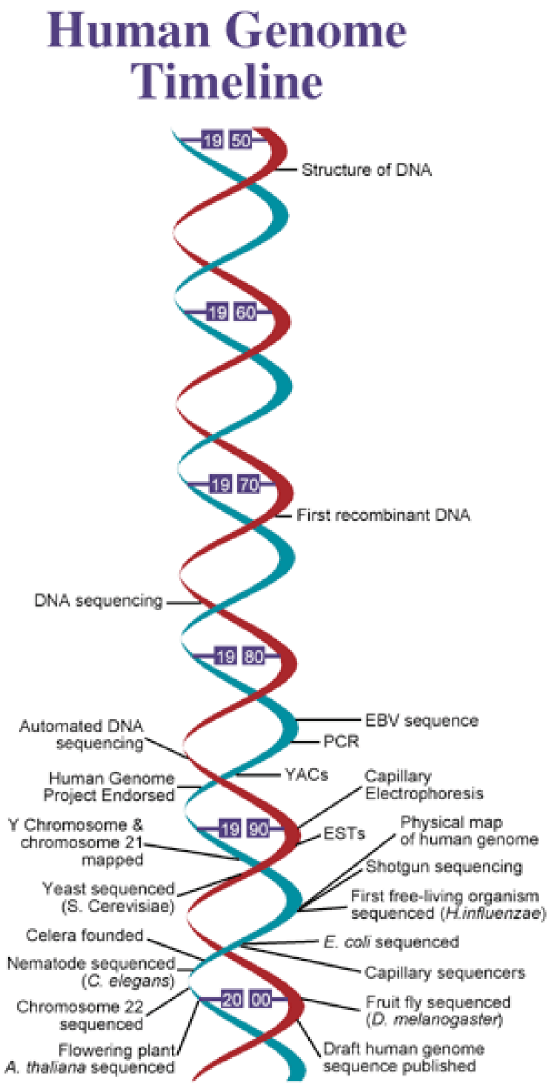
The Sequencing of the Human Genome




The New York Times
National Edition
No. 51,432
TUESDAY, JUNE 27, 2000
tic Code of Human Life Is Cracked by Scientist
The Book of Life
A SHARED SUCC
2 Rivals' Announcem
Marks New Medica
Era, Risks and All
By NICHOLAS WADE

Proposed in 1985 and endorsed in 1988: large coordinated effort between 20 government-sponsored research teams involving hundreds of people: "International Human Genome Sequencing Consortium". Government-funded groups = "the public project."

In 1998, Craig Venter founded a private company "Celera Genomics" and announced that his company planned to complete the sequence of the genome within 3 years, well ahead of the public effort. By automating the entire sequencing process with robotics, a tremendous amount of computing power, and the latest capillary sequencers. Competition between this private venture and the public project became fierce. In 2001, both groups separately published the "draft sequences".

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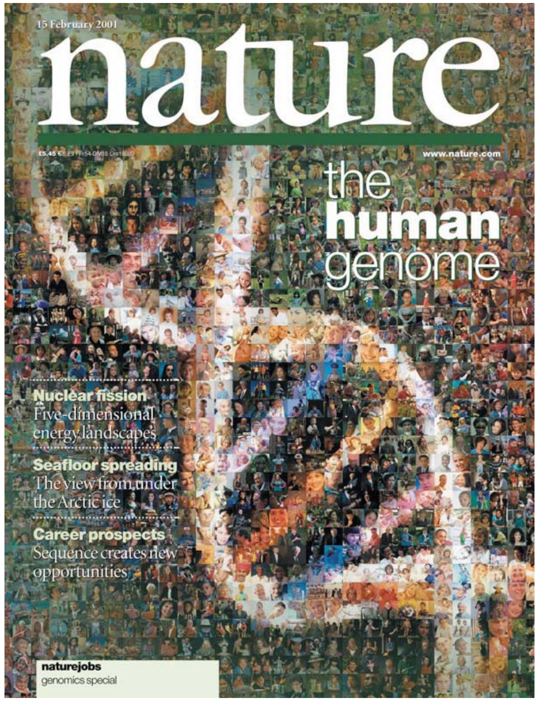
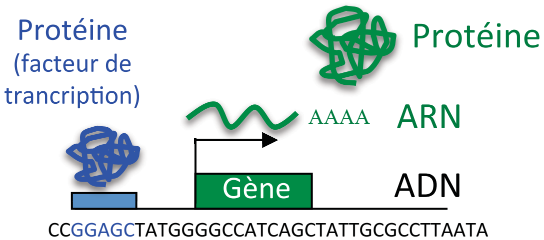
The Sequencing of the Human Genome



Le génome humain : trois milliards de paires de bases, 20 000 gènes



AACTCATCCAGGAATGGGCCCTACGTACCGTAACGTTGCAAATTCAGTCGGTACGTTTCCAGG
CTACACACACACTGACAGATAGACAGATTGTCGTGTTATVTGACTTGGAACTGTAGGCCCTTGA
ATCTTGGCAGTCGTAACGTACGTACGGTACTGGTAACGTGAGGTCAGGTTGTTGATTACCAGGA
TCTACTAGAAGAAAAATTGGGCCCTACGTACCGTAACGTTGCAAATTCAGTCGGTACGTTTCCA
GGCTACACACACACTGACAGATAGACAGATTGTCGTGTTATVTGACTTGGAACTGTAGGCCCTT
GAATCTTGGCAGTCGTAACGTACGTACGGTACTGHEARTDISETGTTCAACTCATCCAGGAAAAT

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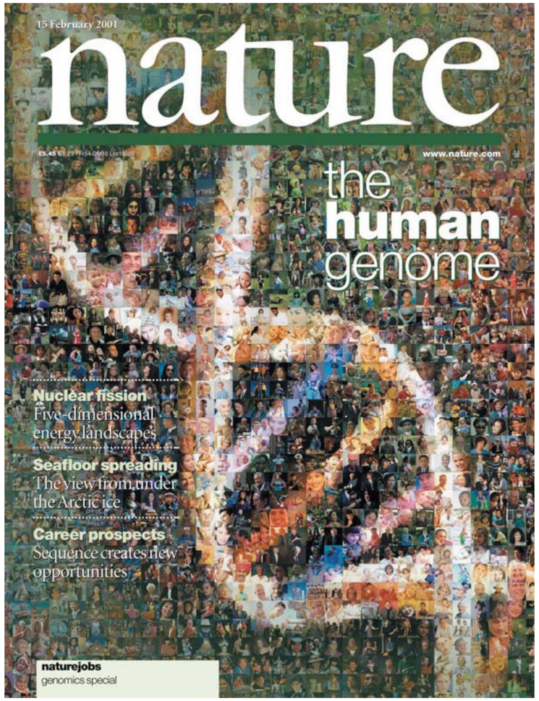
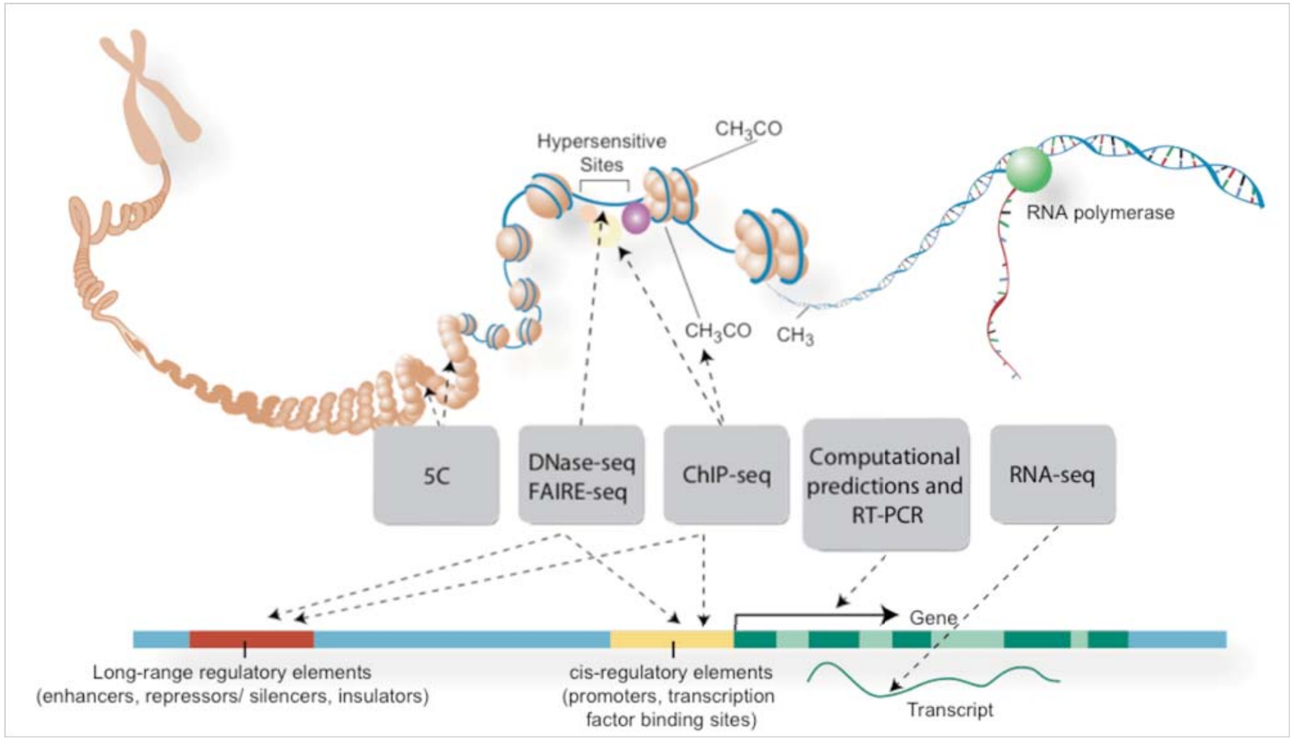
Deciphering the Human Genome

Understanding the genome… and how it is interpreted:





Three billion DNA base pairs

20,000 protein-coding genes

Transcribed regions
Regulatory DNA sequence elements of genes
Transcription Factor DNA binding sites
DNA methylation
Chromatin accessibility, modifications
Chromatin 3D organization

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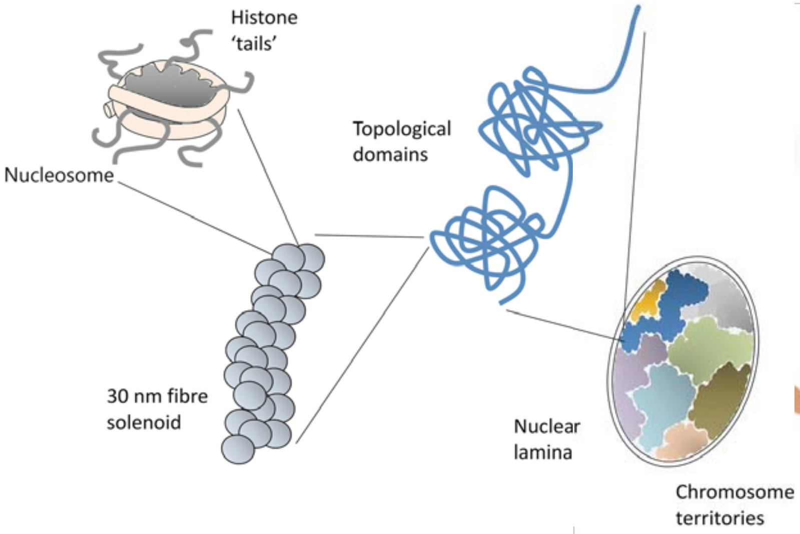
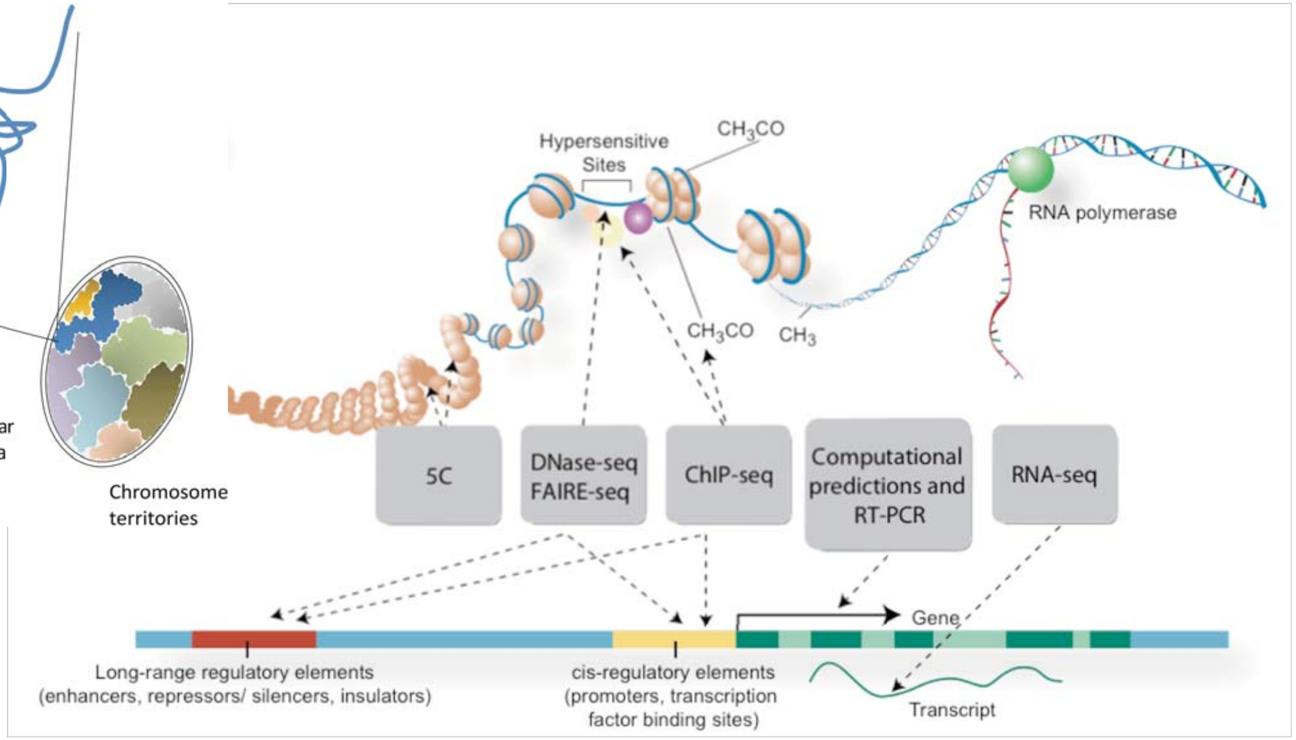
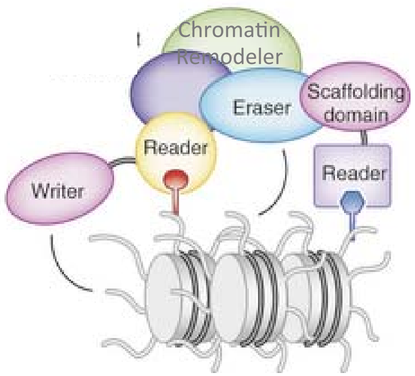
From Human Genome to Epigenomes







Transcribed regions
Regulatory DNA sequence elements of genes
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DNA methylation
Chromatin accessibility, modifications
Chromatin 3D organization

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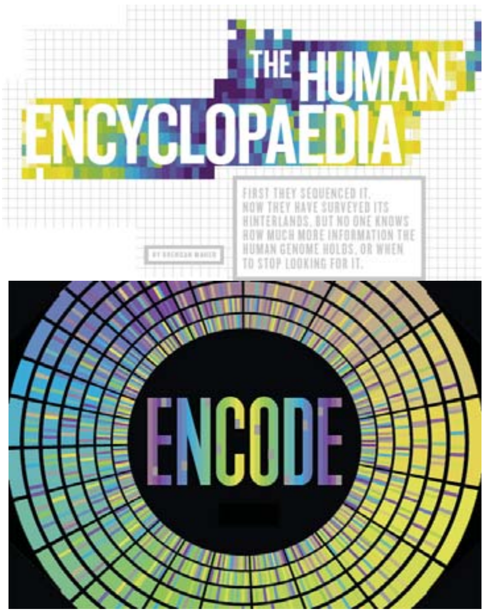
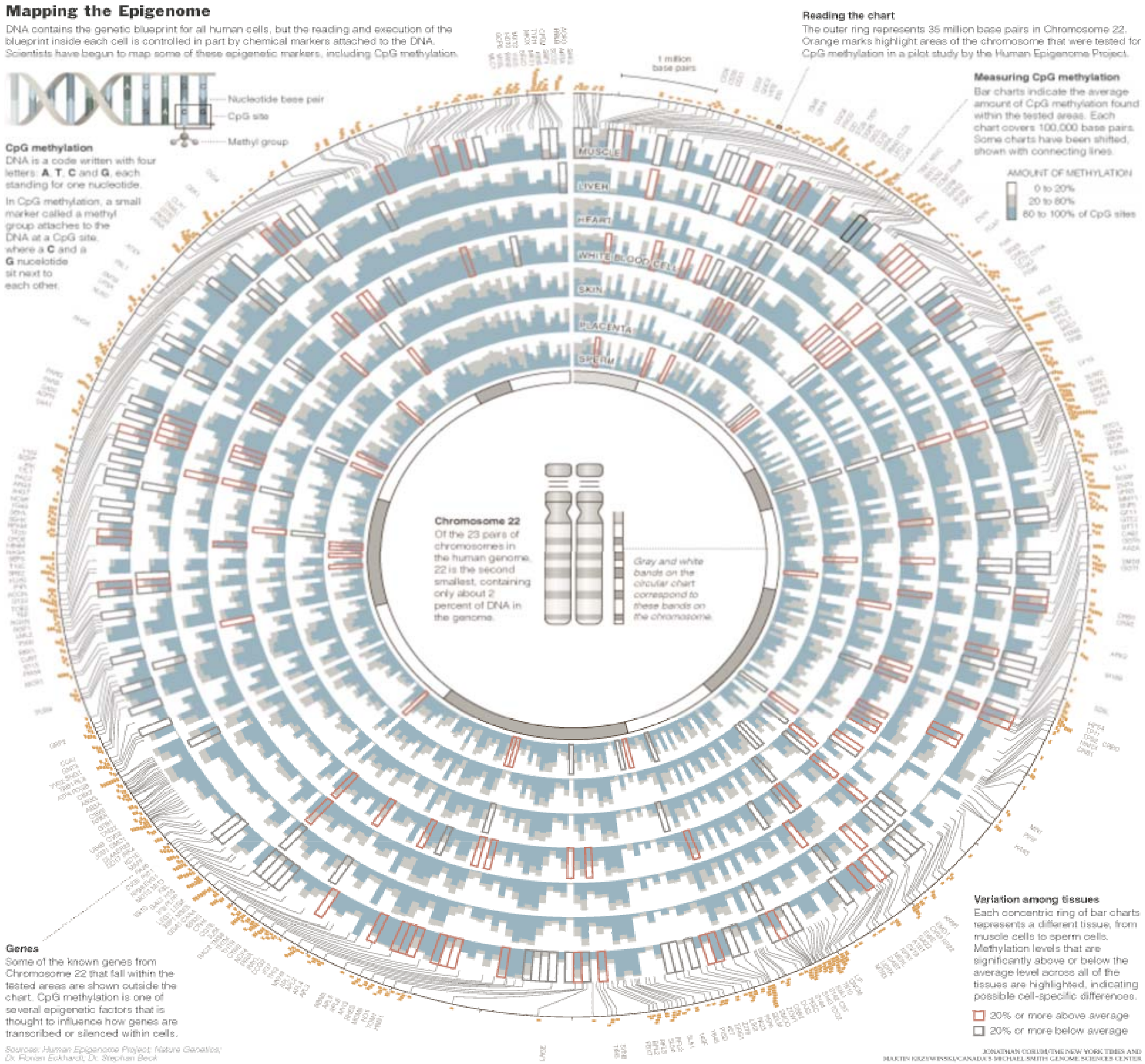
From Human Genome to Epigenomes

An integrated encyclopedia of DNA elements in the human genome

The ENCODE Project Consortium*

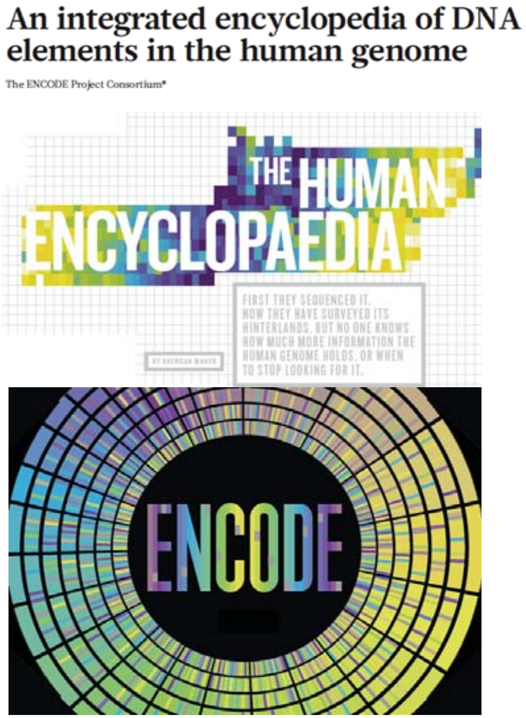


Nature, September 2012

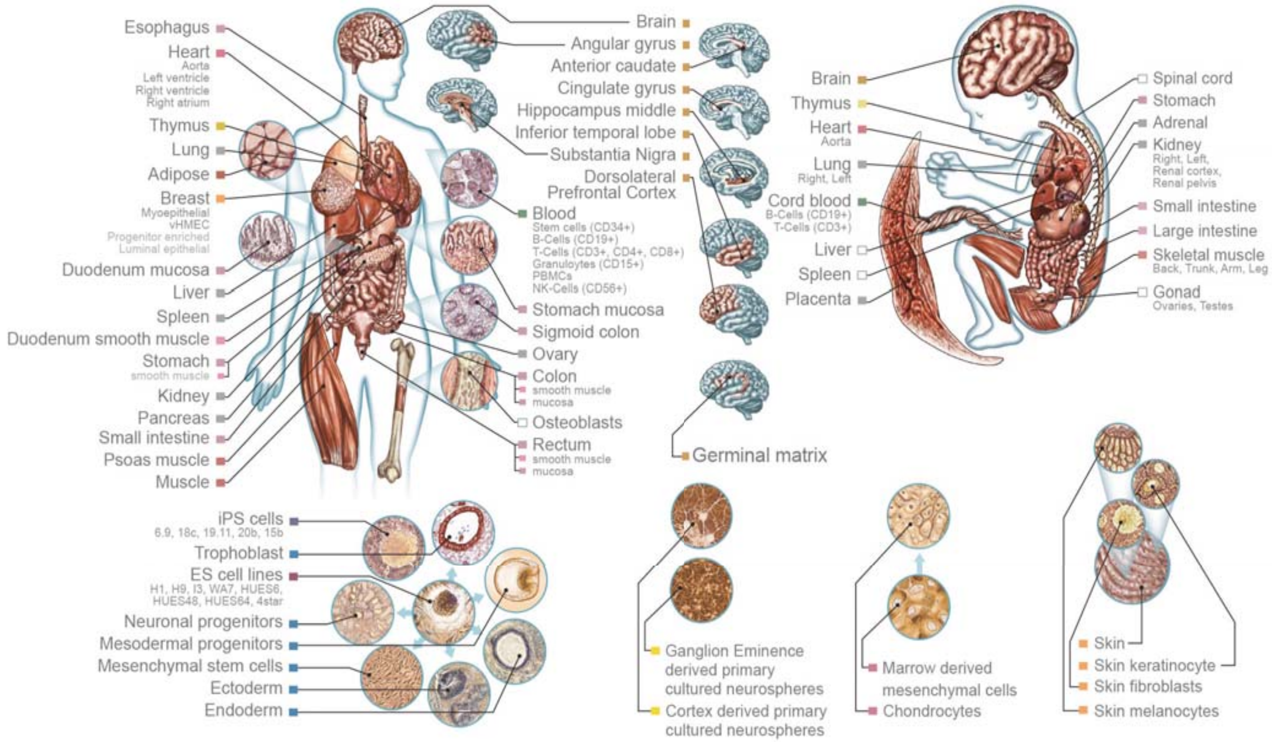


E. Heard, 2016

From Human Genome to Epigenomes



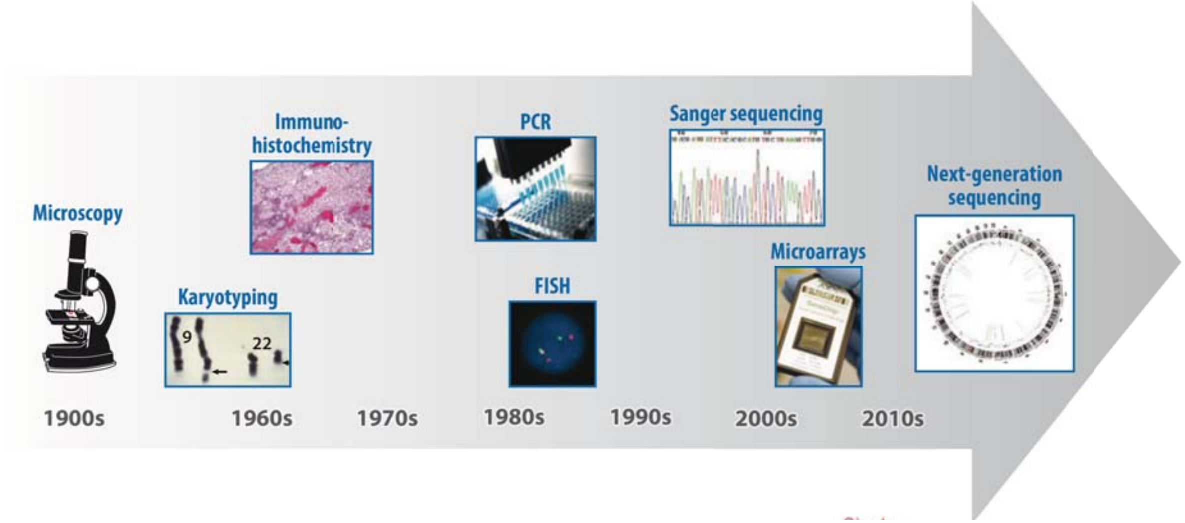
Nature, September 2012



NIH Roadmap Epigenomics Program: to systematically characterize epigenomic landscapes in primary human tissues and cells. Reference epigenomes are available for more than 100 cell and tissue types.

111 reference human epigenomes generated as part of the programme, profiled for histone modification patterns, DNA accessibility, DNA methylation and RNA expression. We establish global maps of regulatory elements, define regulatory modules of coordinated activity, and their likely activators and repressors. We show that disease- and trait-associated genetic variants are enriched in tissue-specific epigenomic marks, revealing biologically relevant cell types for diverse human traits, and providing a resource for interpreting the molecular basis of human disease.

Cancer: from Boveri to Venter



- In 2007 - oligonucleotide 'baits" to capture (enrich for) specific portions of the genome eg the ~2% of genomic DNA containing exons – protein coding portion (**whole "exome" seq: WES**): widely used because cheaper – identified all the known and some new genes in cancer but *missed the "non-coding" part of the genome* including regulatory regions and promoters, as well as chromosomal events, epigenome –wide effects…

- Massive Parallel Sequencing (MPS) (see Bentley et al, 2008) - by 2012 > 600 billion bp/run…

- MPS enabled **whole genome sequencing** (**WGS**) and the use of a single technology platform for all categories of genome analysis: detecting point mutations, structural variations, transcriptomes (RNA Seq), DNA methylomes, chromatin structure (ChIP-Seq)

- Has been remarkable in centering efforts from various fields – but has also highlighted our basic ignorance about cancer biology!

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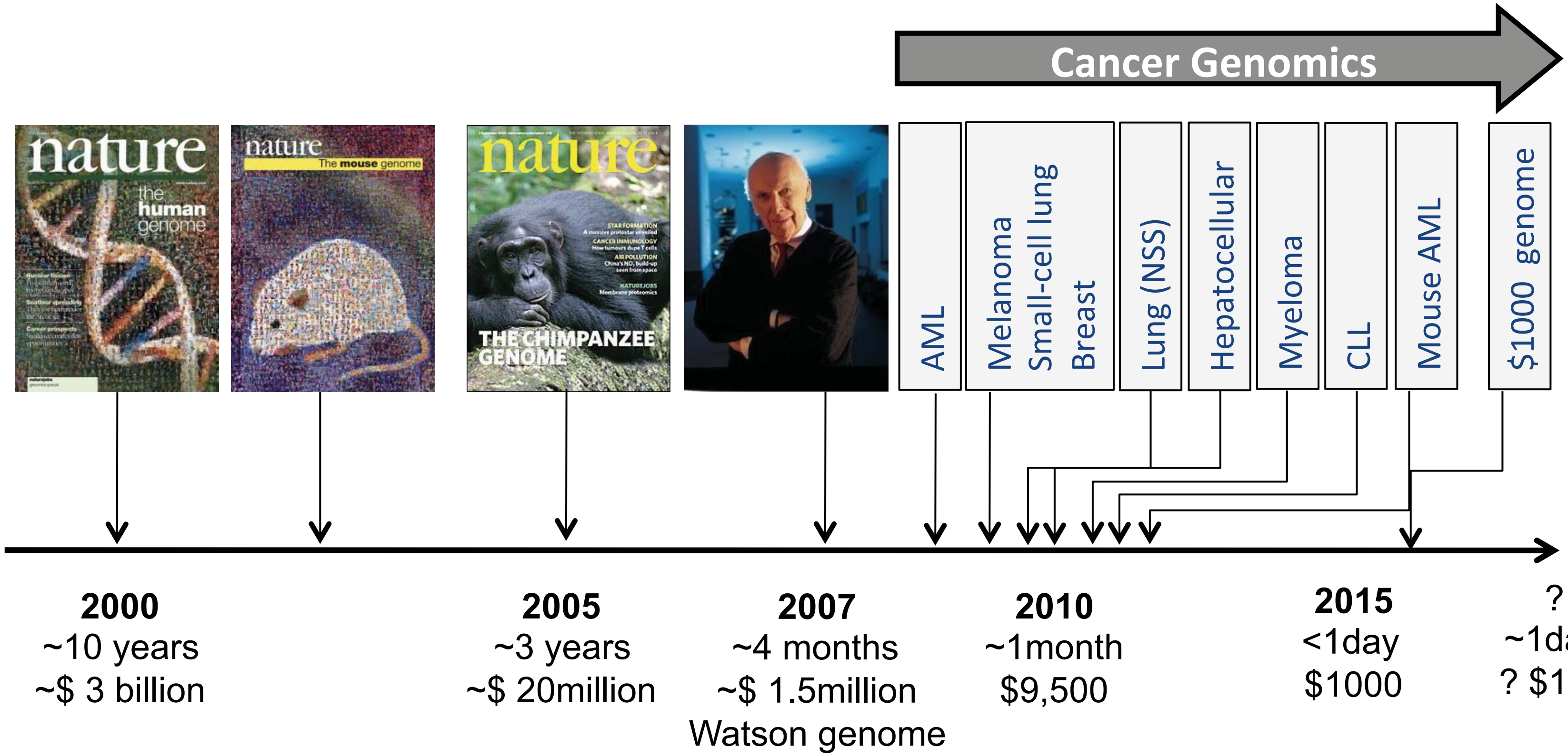
Cost of Sequencing Genomes



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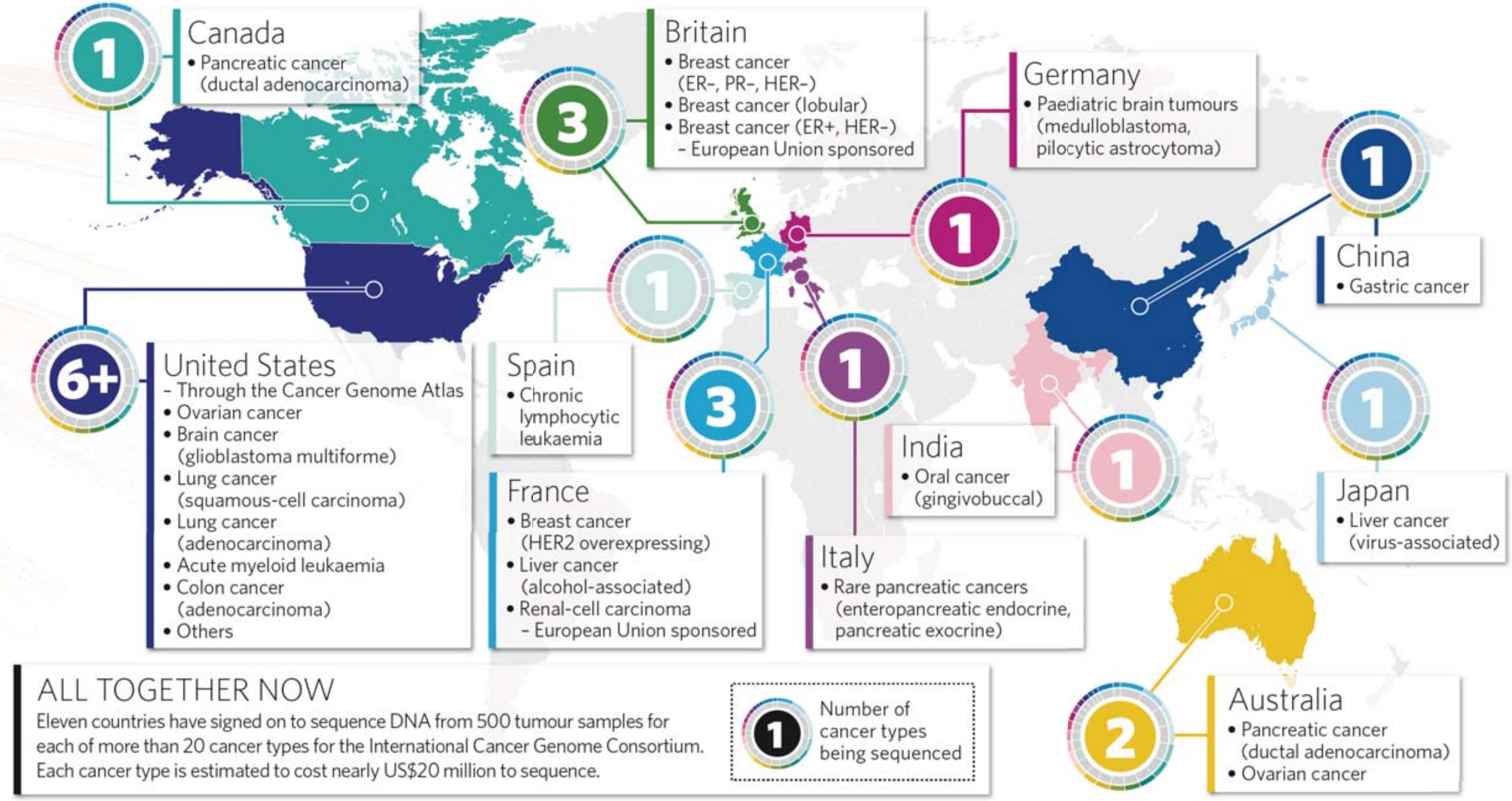
Sequencing Cancer Genomes

International Cancer Genome Consortium **(ICGC)**, formed in 2008, to coordinate efforts to sequence 500 tumors from each of 50 cancers. Total cost in the order of US$1 billion.

The ICGC included two older, large scale projects: the **Cancer Genome Project**, at the **Wellcome Trust Sanger Institute** (UK), and the US **National Institutes of Health's Cancer Genome Atlas** (**TCGA**) (http://cancergenome.nih.gov/)



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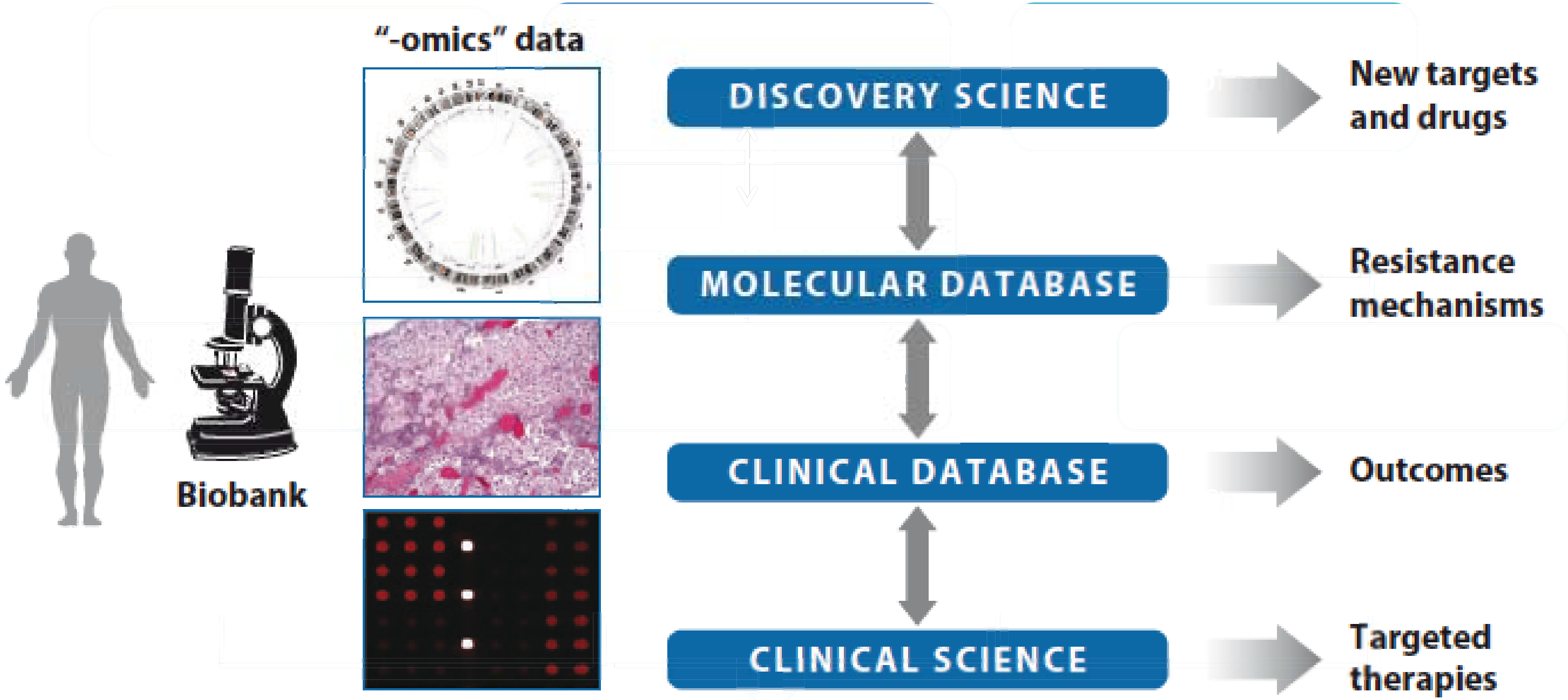
Analysing cancer genomes



- Hypothesis-driven cancer research
- Novel clinically relevent cancer specific changes
- New signatures enabling tumour classification
- Targeted drug and therapeutic strategies
- Towards peronalised medicine

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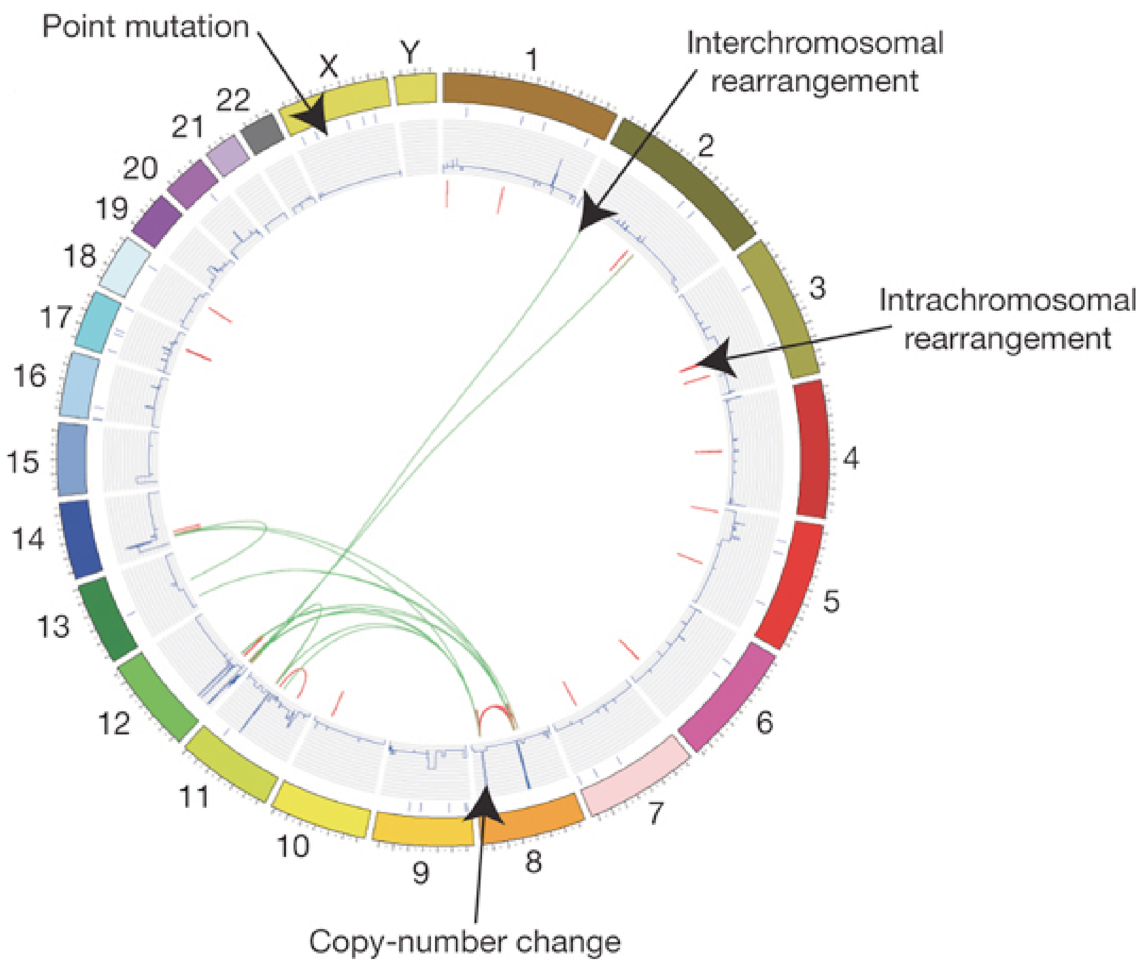
Analysing cancer genomes

"The Cancer Genome"
Michael R. Stratton, Peter J. Campbell & P. Andrew Futreal (2009)
Nature 458, 719-724



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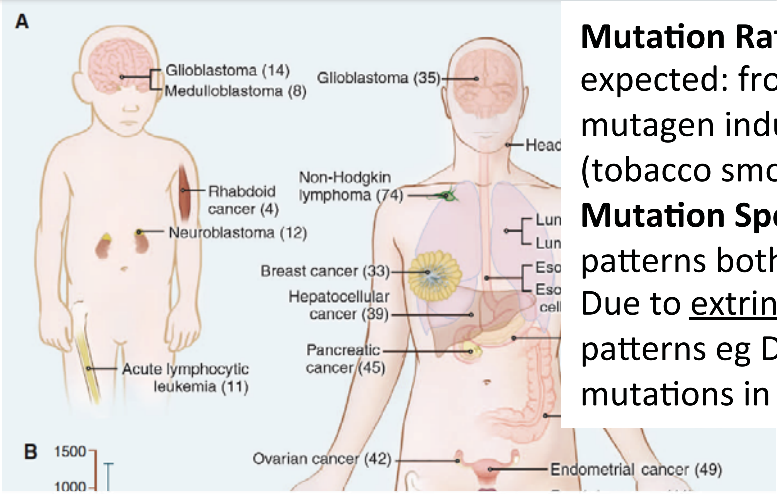
Sequencing Cancer Genomes

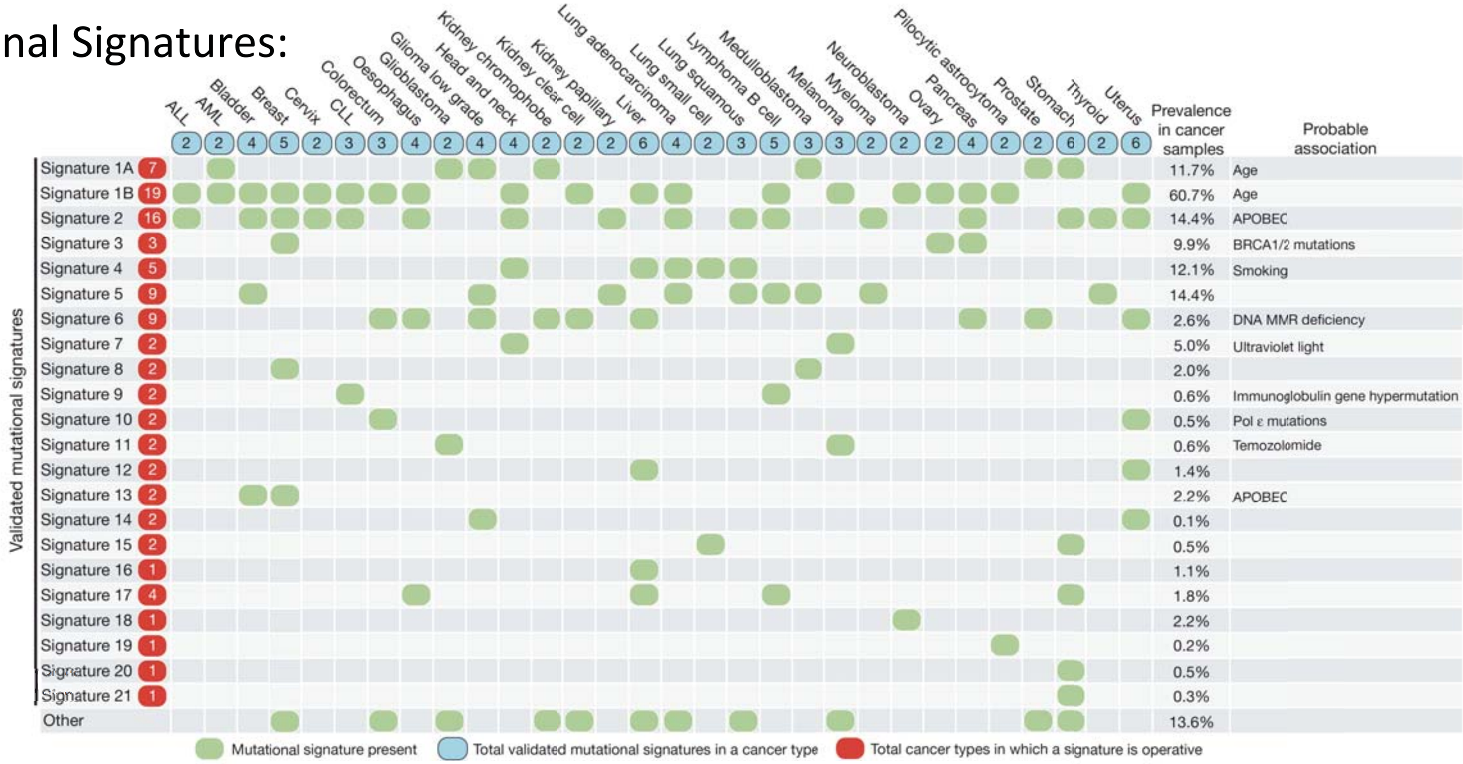
Lessons from cancer genomes



Mutation Rates – much more variable than expected: from <0.1/Mb to ~100/Mb (in mutagen induced tumors eg lung cancer (tobacco smoke), melanoma (UV)

Mutation Spectra – wide array of mutational patterns both across and within tumor types: Due to <u>extrinsic</u> factors (UV, tobacco) or <u>intrinsic</u> patterns eg DNA repair defects (MLH/MSH mutations in colorectal and other cancers);

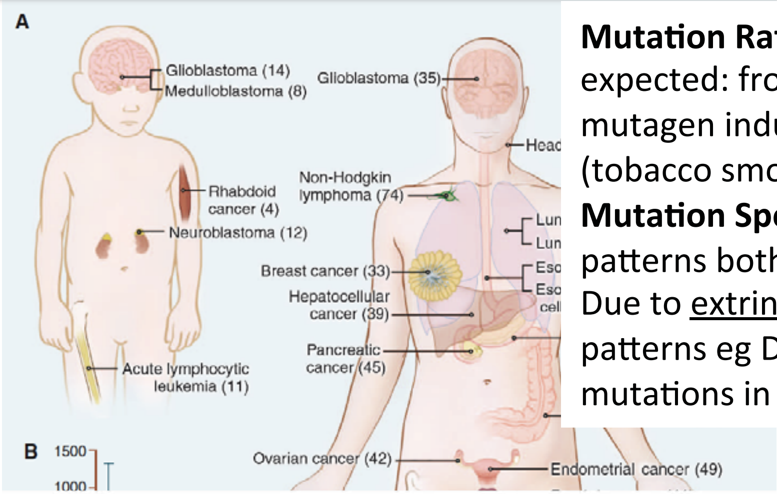
Mutational Signatures:



Vogelstein et al,

E. Heard, 2016

Lessons from cancer genomes



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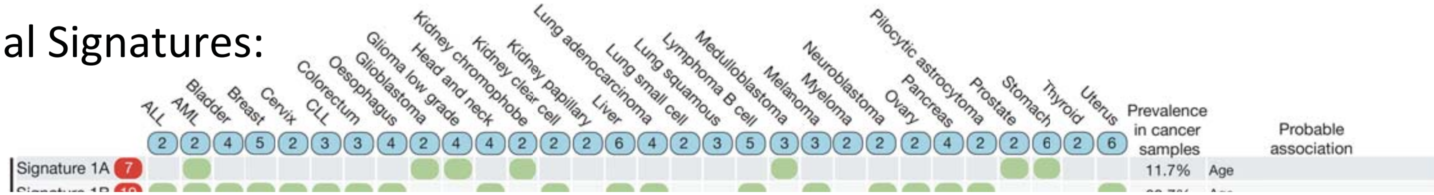
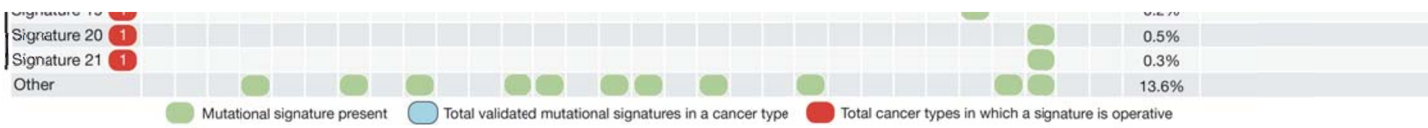


For example, non-small-cell lung tumors (NSCLCs) from heavy cigarette smokers display a preponderance of C > A transversions and significantly more copy number gains and mutations compared with non-smokers (Govindan et al., 2012; Huang et al., 2011; Pleasance et al., 2010)

Colorectal cancers with endogenous mismatch repair deficiency exhibit an enrichment of C > T transitions, particularly at CpG sites, and generally show low levels of chromosomal alterations.



Vogelstein et al,

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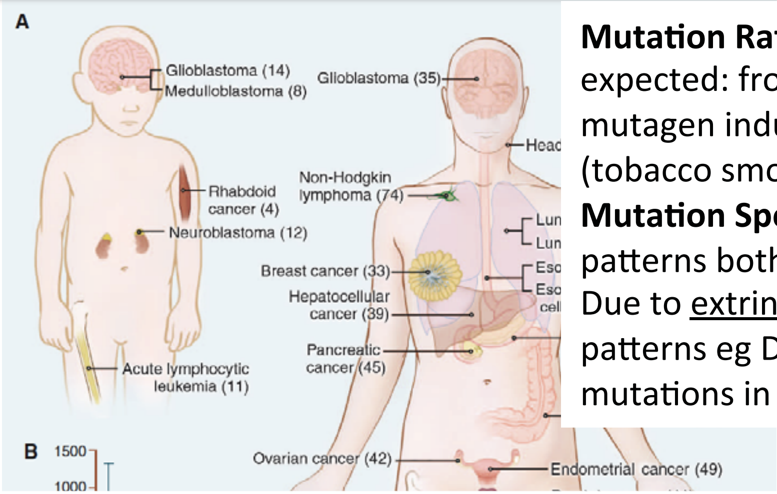
Lessons from cancer genomes



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Mut

Published online 29 October 2014 — *Nucleic Acids Research, 2015, Vol. 43, Database issue* **D805–D811**
doi: 10.1093/nar/gku1075

COSMIC: exploring the world's knowledge of somatic mutations in human cancer

Simon A. Forbes*, David Beare, Prasad Gunasekaran, Kenric Leung, Nidhi Bindal, Harry Boutselakis, Minjie Ding, Sally Bamford, Charlotte Cole, Sari Ward, Chai Yin Kok, Mingming Jia, Tisham De, Jon W. Teague, Michael R. Stratton, Ultan McDermott and Peter J. Campbell

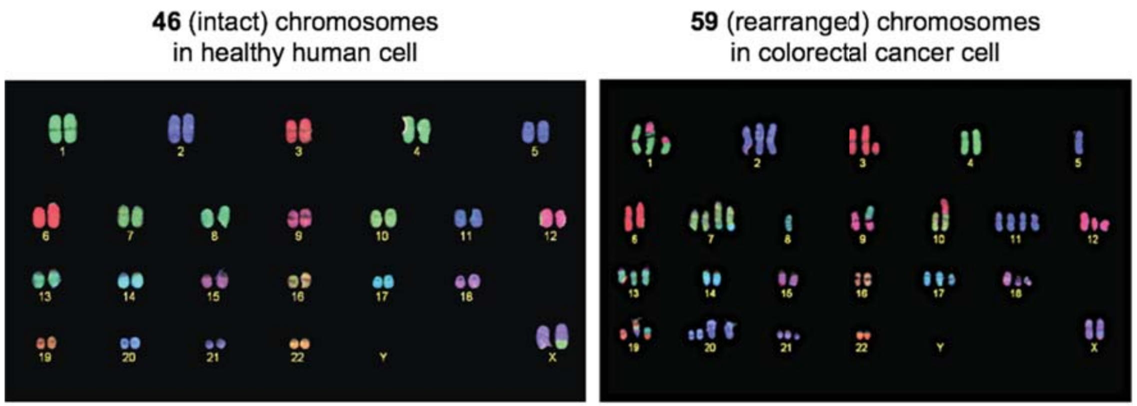
Cancer Genome Project, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK, CB10 1SA.

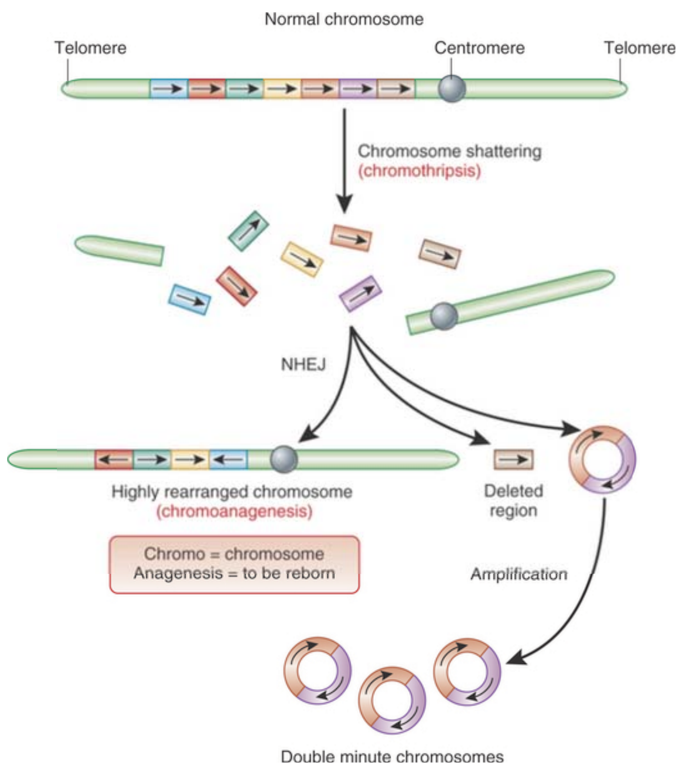
COSMIC, the Catalogue Of Somatic Mutations In Cancer (http://cancer.sanger.ac.uk) is the world's largest and most comprehensive resource for exploring the impact of somatic mutations in human cancer

Vogelstein

E. Heard, 201

Lessons from cancer genomes





Mutation Rates – much more variable than expected: from <0.1/Mb to ~100/Mb (in mutagen induced tumors eg lung cancer (tobacco smoke), melanoma (UV)

Mutation Spectra – wide array of mutational patterns both across and within tumor types:

Chromosomal Gains & Losses – aneuploidy (as expected from classic cytogenetics). Typical tumor exhibits large gains/losses affecting 25% of its genome plus 10% focal events (deletions, amplifications – though driver gene often not yet assigned definitively)

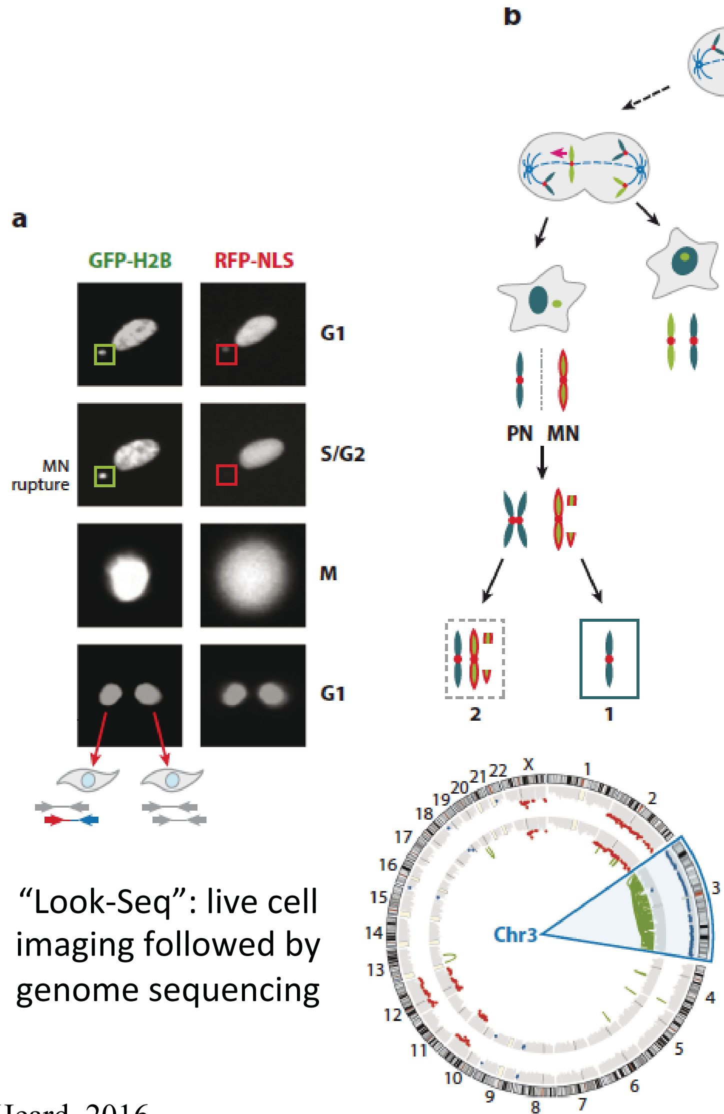
Chromosomal Shattering (chromothripsis) – surprise discovery of catastrophic phenomena producing tens/hundreds of rearrangement affecting just one or a few chromosomes (Stephens et al, 2011), in different tumor types – bone, pediatric medulloblastoma, neuroblastoma. Now know that is is sometimes due to mis-segregated chromosomes in micronuclei that undergo premature condensation, pulverisation and rearrangement and may then reincorporated at the next cell cycle…) (Zhang et al, Nature 2015)

Chromplexy – copy neutral chromosomal chains of rearrangements, in prostate cancers

E. Heard, 2016

Chromothripsis: A New Mechanism for Rapid Karyotype Evolution

From: *Mitchell L. Leibowitz, Cheng-Zhong Zhang, and David Pellman Ann Rev Gen. 2015*



"Look-Seq": live cell imaging followed by genome sequencing

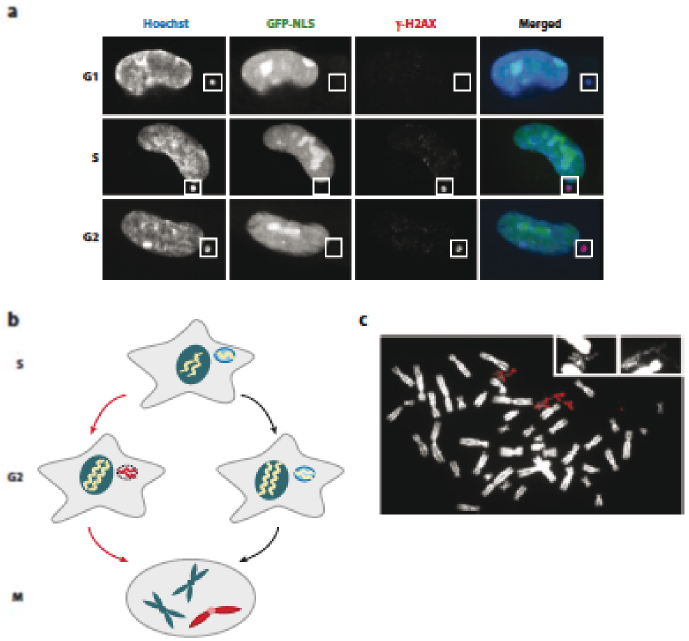
ARTICLE

doi:10.1038/nature14493

Chromothripsis from DNA damage in micronuclei

Cheng-Zhong Zhang, Alexander Spektor, Hauke Cornils, Joshua M. Francis, Emily K. Jackson, Shiwei Liu, Matthew Meyerson & David Pellman

Nature 2015



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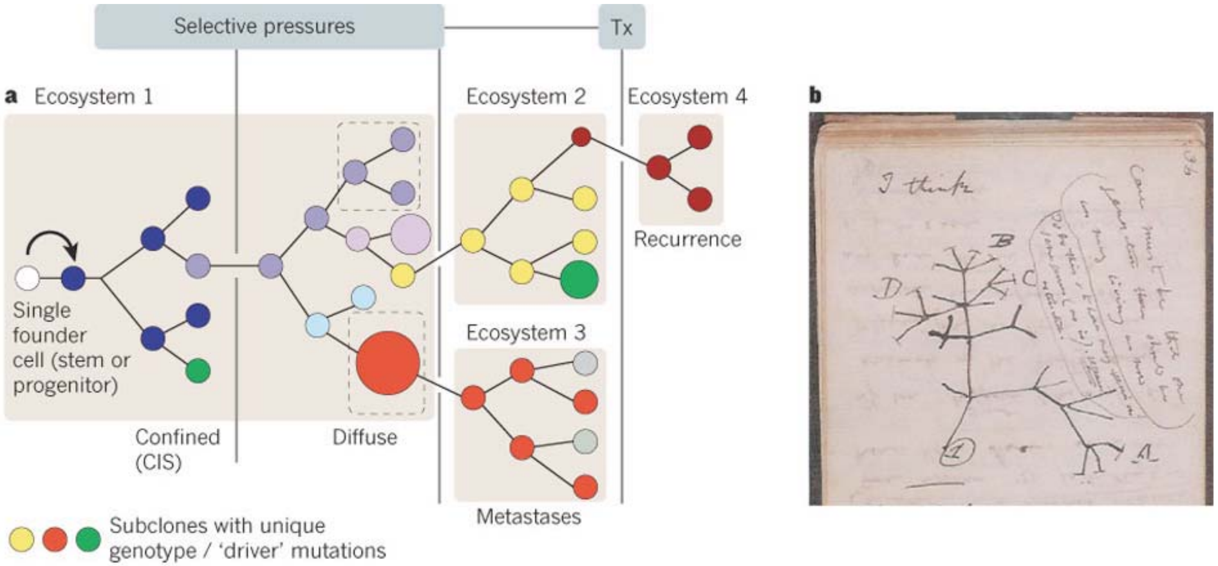
Tumor Evolution?



Rather than the gradual appearance of mutations and natural selection (Darwinian model), massive events such as chromothripsis can also occur, generating several genomic lesions in one "big leap" with potential to drive cancer (macro-evolution)…

"Hopeful Monsters" – chromosomal rearrangements that usually lead to death but occasionally give rise to something "greater" (Goldsmith)

La théorie des monstres prometteurs

Gerlinger et al. (
Nature Genetics

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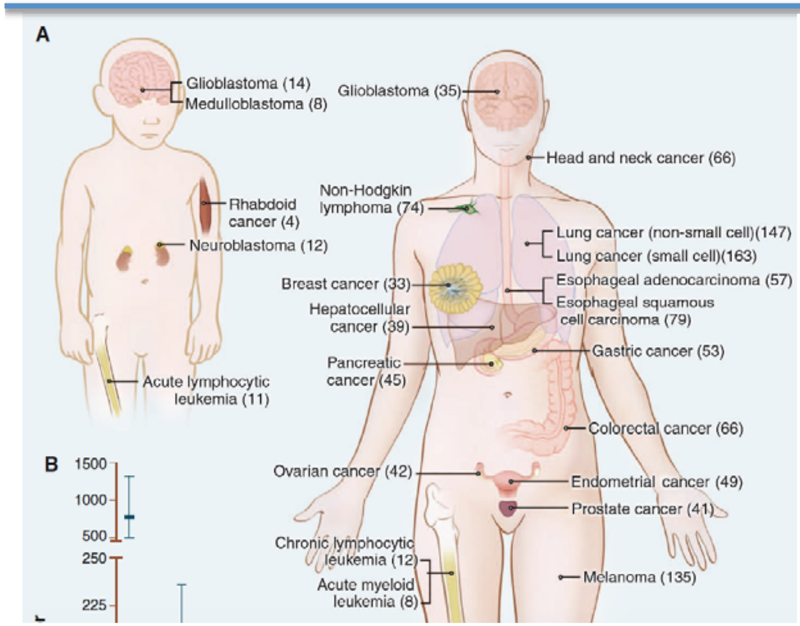
Lessons from cancer genomes

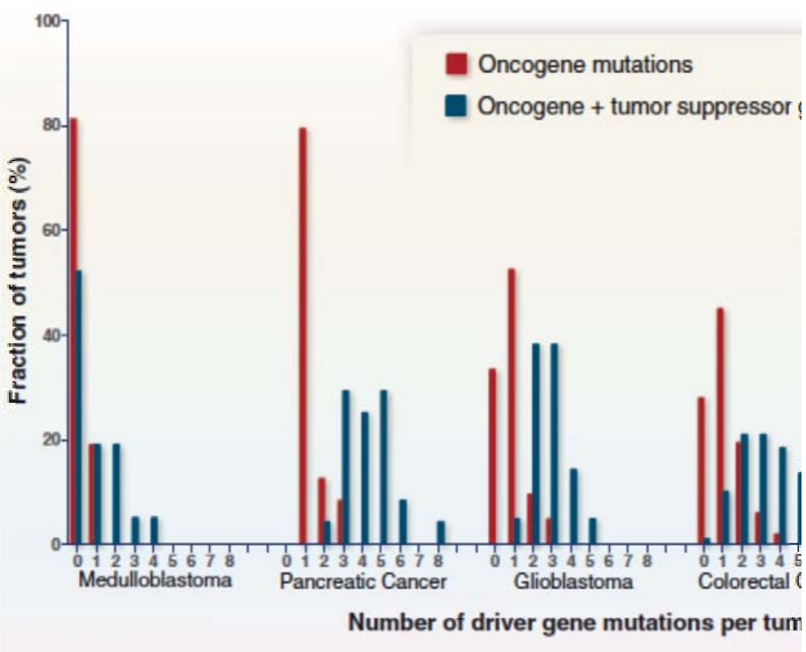


New Cancer Genes?

According to Vogelstein (Science 2013):

- ~140 genes that "drive" tumorigenesis
- Classified into 12 signalling pathways that regulate 3 core processes: cell fate, cell survival and genome maintenance
- Typical tumor contains 2-8 such "driver" gene mutations
- Rest are just passengers…?

BUT – genes <20% mutated ("tails") can be useful to identify redundant mutations in a given signaling path, or else new pathway…



Some cancers had no/few mutations in any *known* cancer genes…

⇒ Mutational screening may not be worthwhile?

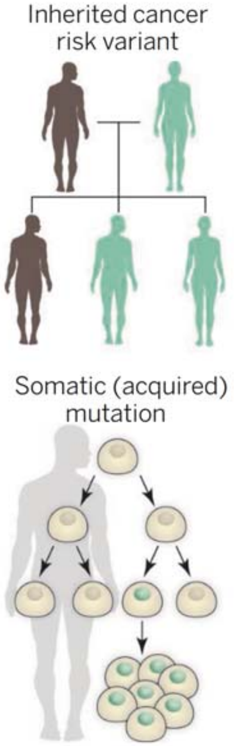
⇒ Non-coding sequence mutation -> aberrant activation and silencing of cancer genes?

⇒ Epimutations? (DNA methylation or chromatin change?)

⇒ In *cis*: may implicate regulatory elements and/or epimutations? In *trans*: mutations or mis-targeting of Epigenetic Regulatory factors….?

-

Discoveries from the Non-Coding Cancer Genomes



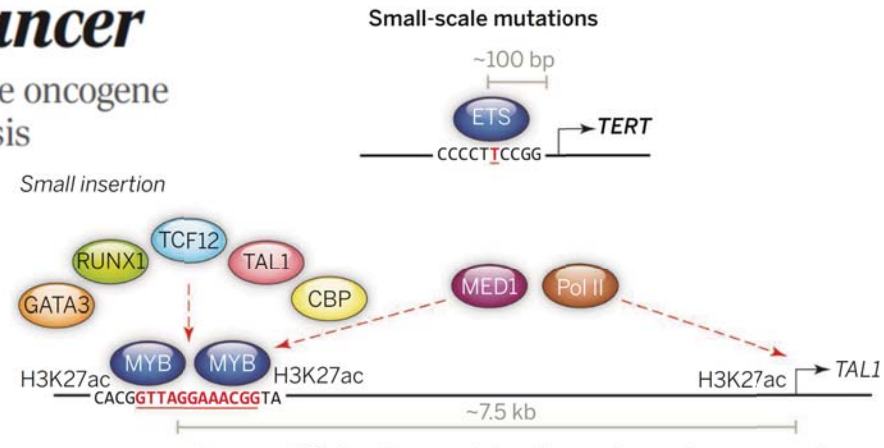
Genetics of cancer. Both inherited variants (**top**) and acquired mutations (**bottom**) can contribute to tumorigenesis.

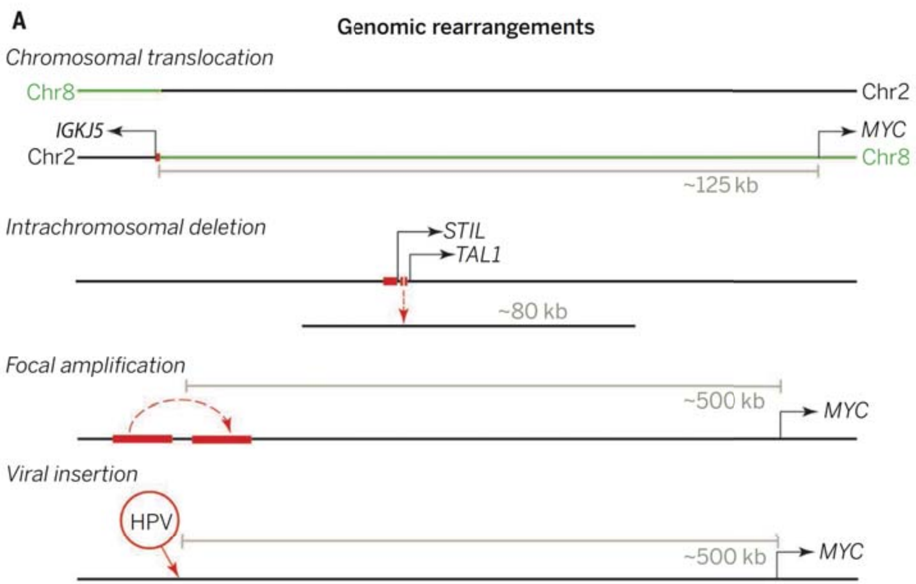
Cancer by super-enhancer

Tiny changes in our genomes can enhance oncogene expression and contribute to tumorigenesis

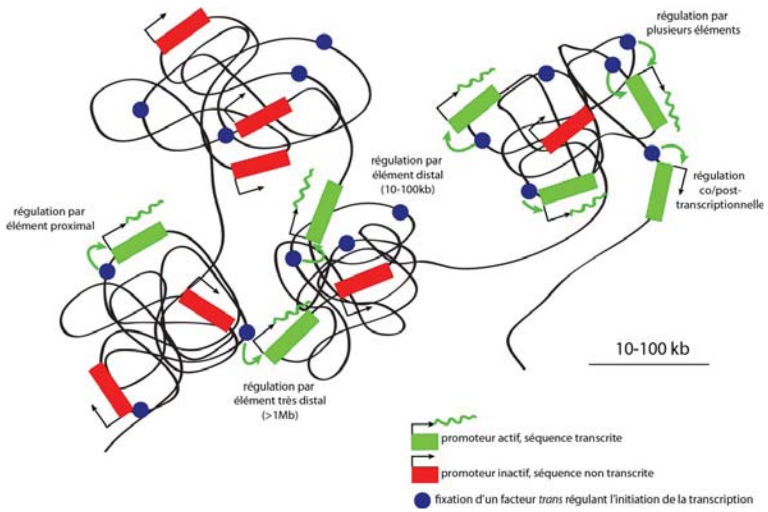
An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element

Marc R. Mansour,[1,2] Brian J. Abraham,[3*] Lars Anders,[3*] Alla Berezovskaya,[1] Alejandro Gutierrez,[1,4] Adam D. Durbin,[1] Julia Etchin,[1] Lee Lawton,[3] Stephen E. Sallan,[1,4] Lewis B. Silverman,[1,4] Mignon L. Loh,[5] Stephen P. Hunger,[6] Takaomi Sanda,[7] Richard A. Young,[3,8]† A. Thomas Look[1,4]†





Discoveries from the Non-Coding Cancer Genomes

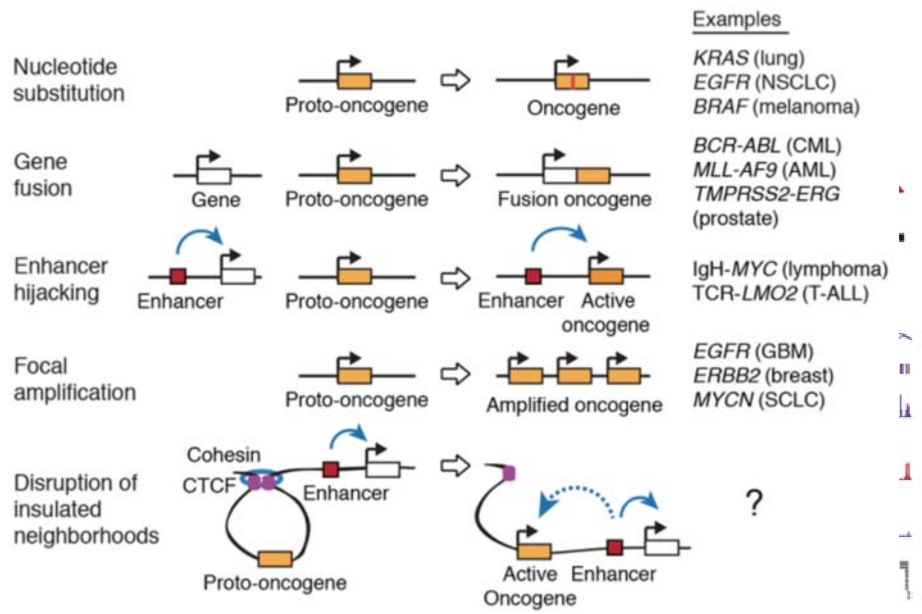


Science REPORTS

Cite as: D. Hnisz *et al.*, *Science* 10.1126/science.aad9024 (2016).

Activation of proto-oncogenes by disruption of chromosome neighborhoods

Denes Hnisz,[1*] Abraham S. Weintraub,[1,2*] Daniel S. Day,[1] Anne-Laure Valton,[3] Rasmus O. Bak,[4] Charles H. Li,[1,2] Johanna Goldmann,[1] Bryan R. Lajoie,[3] Zi Peng Fan,[1,5] Alla A. Sigova,[1] Jessica Reddy,[1,2] Diego Borges-Rivera,[1,2] Tong Ihn Lee,[1] Rudolf Jaenisch,[1,2] Matthew H. Porteus,[4] Job Dekker,[3,6] Richard A. Young[1,2†]

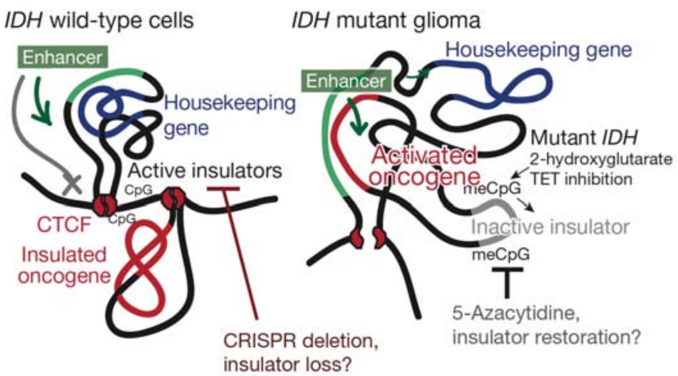


LETTER

doi:10.1038/nature16490

Insulator dysfunction and oncogene activation in *IDH* mutant gliomas

William A. Flavahan[1,2,3*], Yotam Drier[1,2,3*], Brian B. Liau[1,2,3], Shawn M. Gillespie[1,2,3], Andrew S. Venteicher[1,2,4], Anat O. Stemmer-Rachamimov[1], Mario L. Suvà[1,2] & Bradley E. Bernstein[1,2,3]



E.

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Discoveries from the Non-Coding Cancer Genomes

Subtle mutations affecting regulatory or chromosome structural elements, sometimes at very long distance (100s kilobases) may be sufficient to activate "oncogenes" or inactivate tumor suppressors

More Discoveries from Cancer Genomes

Table 2. Discoveries from Cancer Genome Characterization

Cellular Process Altered by Genomic Alterations	Examples of Cancer Genes Discovered (or Extended to New Cancers*) by Genomics
RTK signaling	*EGFR*,[a] *ERBB2*,*[,a] *MET*,*[,a] *ALK*,*[,a] *JAK2*,[a] *RET*,*[,a] *ROS*,*[,a] *FGFR1*,*[,a] *FGFR2*,[a] *PDGFRA*,*[,a] and *CRKL*[a]
MAPK signaling (oncogenes)	*KRAS*,*[,a] *NRAS*,*[,a] *BRAF*, [a] and *MAP2K1*[a]
MAPK signaling (TSG)	*NF1**[,b]
PI3K signaling (oncogenes)	*PIK3CA*,[a] *AKT1*,[a] and *AKT3*[a]
PI3K signaling (TSG)	*PTEN**[,b] and *PIK3R1*[b]
Notch signaling (oncogene or TSG)	*NOTCH1*,[c] *NOTCH2*,[c] and *NOTCH3*[b]
TOR signaling (TSG)	*STK11*,*[,b] *TSC1*,*[,b] and *TSC2**[,b]
Wnt/β-catenin signaling (TSG)	*APC**[,b] and *CTNNB1**[,a]
TGF-β signaling (TSG)	*SMAD2*,*[,b] *SMAD4*,*[,b] and *TGFBR2*[b]
NF-κB signaling (oncogene)	*MYD88*[a]
Other signaling	*RAC1*,[a] *RAC2*,[a] *CDC42*,[a] *KEAP1*,[b] *MAP3K1*,[b] *MAP2K4*,[b] *ROBO1*,[b] *ROBO2*,[b] *SLIT2*,[b] *SEMA3A*,[b] *SEMA3E*,[b] *ELMO1*,[d] and *DOCK2*[d]
Epigenetics DNA methylation	*DNMT3A*[b]
Epigenetics DNA hydroxymethylation	*TET2*[b]
Chromatin histone methyltransferases	*MLL*,*[,b] *MLL2*,[b] *MLL3*,[b] *EZH2*,[c] *NSD1*,[b] and *NSD3*[b]
Chromatin histone demethylases	*JARID1A*,[b] *UTX*,[b] *KDM5A*,[b] and *KDM5C*[b]
Chromatin histone acetyltransferases	*CREBP* [b] and *EP300*[b]
Chromatin SWI/SNF complex	*SMARCA1*,*[,b] *SMARCA4*,[b] *ARID1A*,[b] *ARID2*,[b] *ARID1B*,[b] and *PBRM1*[b]
Chromatin other	*CHD1*,[b] *CHD2*,[b] and *CHD4*[b]
Transcription factor lineage dependency or oncogene	*MITF*,[a] *NKX2-1*,[a] *SOX-2*,[a] *ERG*,[a] *ETV1*,[a] and *CDX2*[a]
Transcription factor other	*MYC*,*[,a] *RUNX1*,[b] *GATA3*,[b] *FOXA1*,[b] *NKX3.1*,[b] *SOX9*,[a] *NFE2L2*,[a] and *MED12*[d]
Splicing	*SF3B1*,[d] *U2AF1*,[d] *SFRS1*,[d] *SFRS7*,[d] *SF3A1*,[d] *ZRSR2*,[b] *SRSF2*,[d] *U2AF2*,[d] and *PRPF40B*[d]
RNA abundance	*DIS3*[d]
Translation/protein homeostasis/ubiquitination	*SPOP*,[d] *FBXW7*,*[,b] *WWP1*,*[,b] *FAM46C*,[d] and *XBP1*[d]
Metabolism	*IDH1*[a] and *IDH2* [a]
Genome integrity	*TP53*,*[,b] *MDM2*,[a] *MSH*,*[,b] *MLH*,*[,b] and *ATM**[,b]
Telomere stability	*TERT* promoter mutations[a]
Cell cycle (oncogene)	*CCND1**[,a] and *CCNE1**[,a]
Cell cycle (TSG)	*CDKN2A*,*[,b] *CDKN2B*,*[,b] and *CDKN1B*[b]
Apoptosis regulation	*MCL1*,[a] *BCL2A1*,[a] and *BCL2L1*[a]

[a]Activating mutation or amplification.
[b]Inactivating mutation or deletion.
[c]Both activating and inactivating genomic events observed.
[d]Effect of mutations on protein function unknown.

Eg high frequency of DNA methylation associated mutations in hematopoietic malignancies:

DNMT3A mutations are found in:
AML (30%)
Myeloproliferative neoplasia (MPN) (7–15%)
Myelodysplastic syndrome (MDS) (8%)

TET2 is frequently mutated in myeloid disease:
AML (7–23%),
Chronic myelomonocytic leukemia (CMML) (50%),
MDS (10–20%)

IDH1/2 mutations found in:
AML (16-19%),
MPN (2-9%)
MDS (3%)

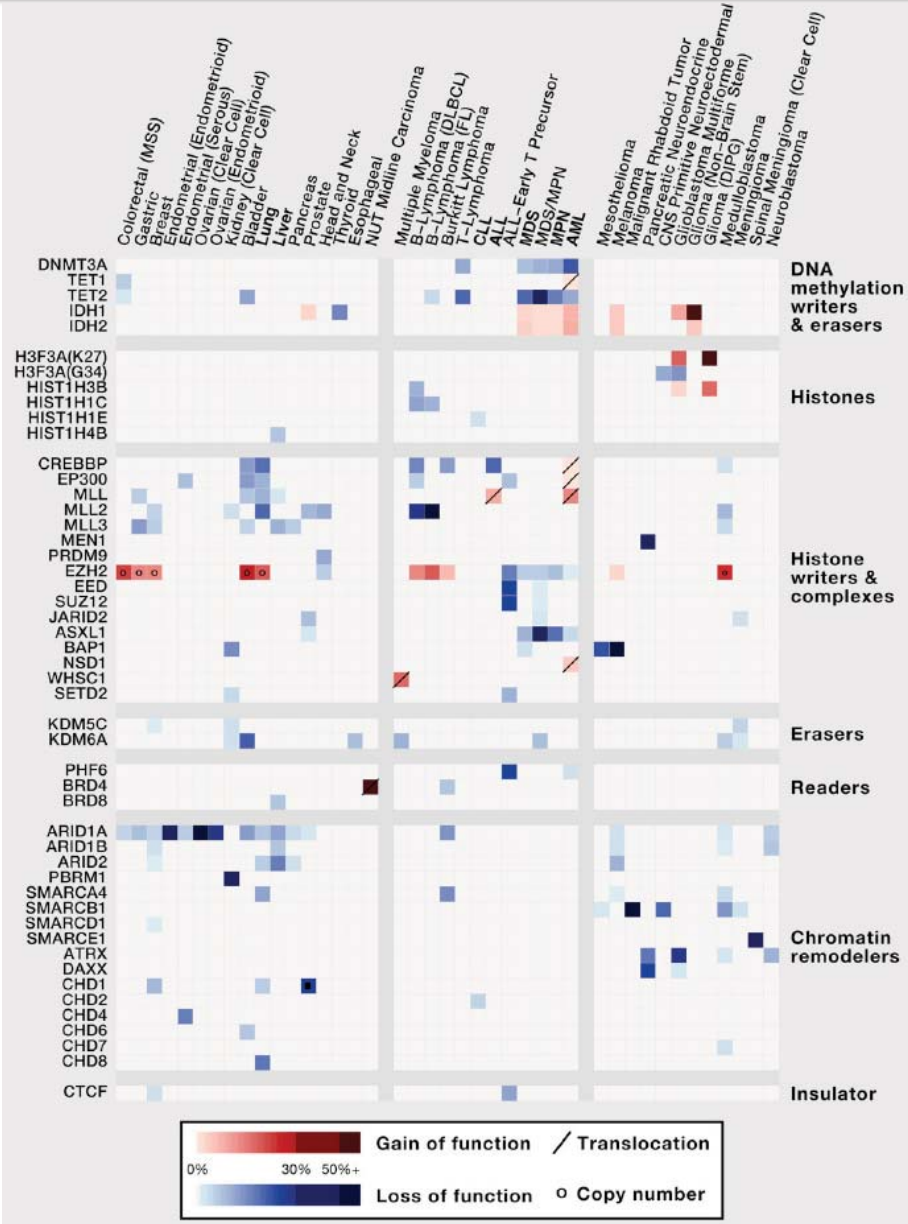
Many Novel Cancer Genes are Involved in Chromatin Functions

Both gain and loss of function found

Already useful for classifying specific tumors!

Affected genes/cell functions still need to be understood…
(Cours IV + V)

Targeted therapy already underway
(Cours VI)



See also: "dbEM: A database of epigenetic modifiers curated from cancerous and normal genomes". Nanda et al, *Scientific Reports* 2016

E. Heard, 2016 *Shen et al, Cell 2013*

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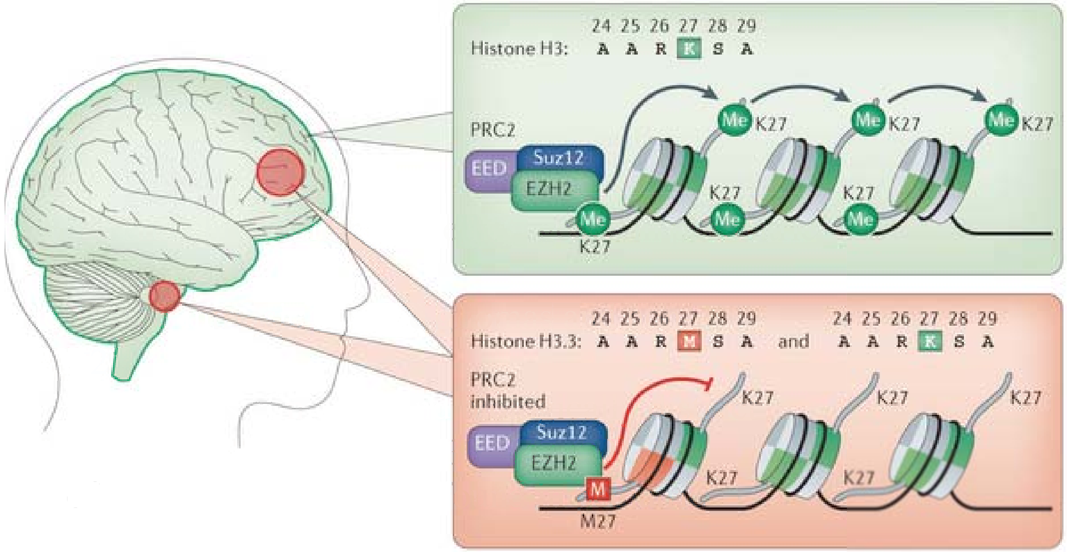
Specific Histone Variants & Modifications

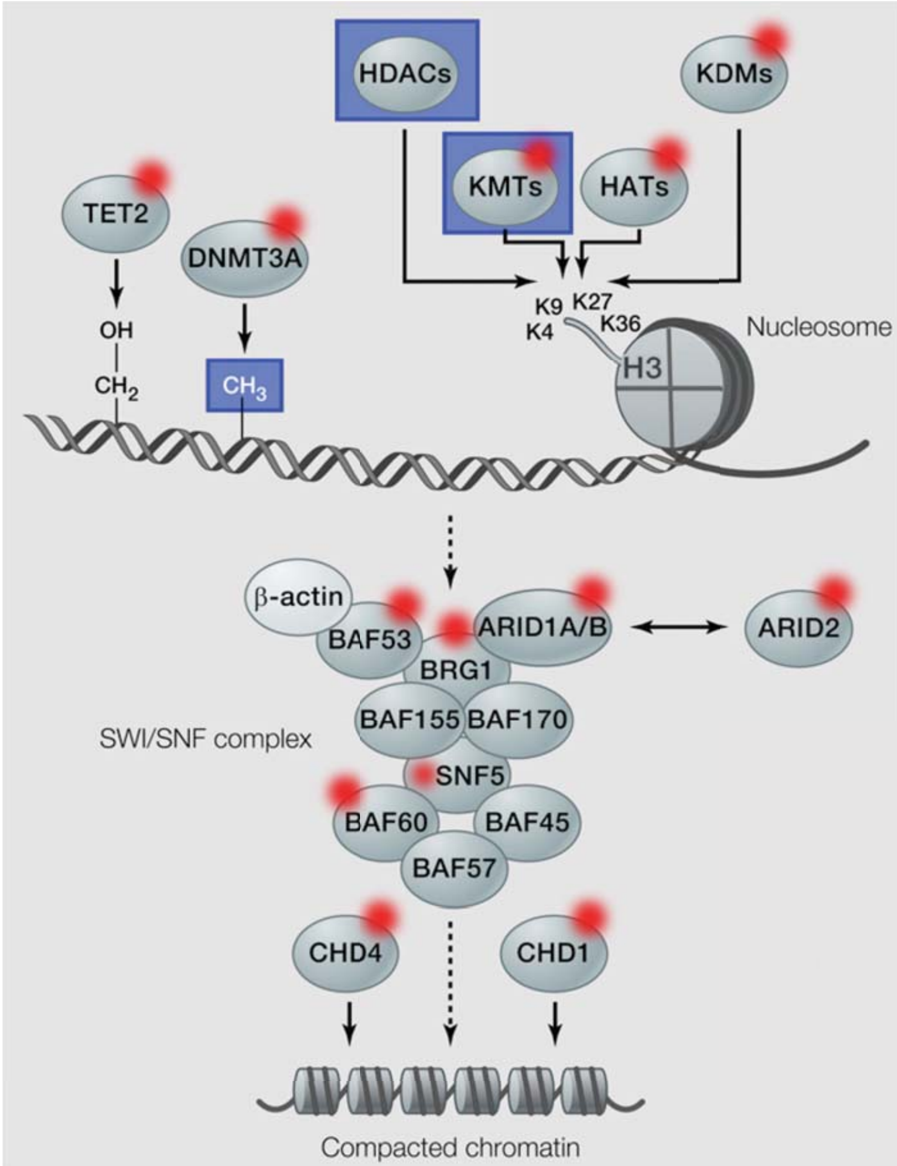
Histone	Number of gene copies	Cell-cycle expression	Mutation and expression pattern	Tumorigenic consequences
H2A.X	1	RI	Reduced expression	Increased cancer progression in p53-knockout mice
H2A.Z	2	RI	Over-expression; oncogene	Numerous cancers
MacroH2A	2	Possibly RI	Reduced expression; tumour suppressor	Melanoma and other cancers
H3.1	10	RD	K27M in H3.1B	Adult and paediatric gliomas, including GBMs and DIPGs, respectively
H3.3	2	RD and RI	K27M, G34R and G34V in H3.3A	Adult and paediatric gliomas, including GBMs and DIPGs, respectively
			K36M in H3.3B	Chondroblastoma
			G34W and G34L in H3.3A	Giant cell tumours in bone
CENP-A	1	RI	Over-expression; oncogene	Numerous cancers

From Maze et al, NRG, 2014

H3.3 Lys 27-to-methionine (K27M) mutation in one of two alleles leads to very specific gliomas. This mutation reprograms epigenetic landscape and gene expression: see genome wide loss in H3K27me3 but specific aberrant enrichment at several hundred genes. This may drive tumorigenesis.
Chan et al, Genes Dev , 2013



Chromatin remodeling proteins, Histone Modifiers and DNA Methyltransferases/demethylases



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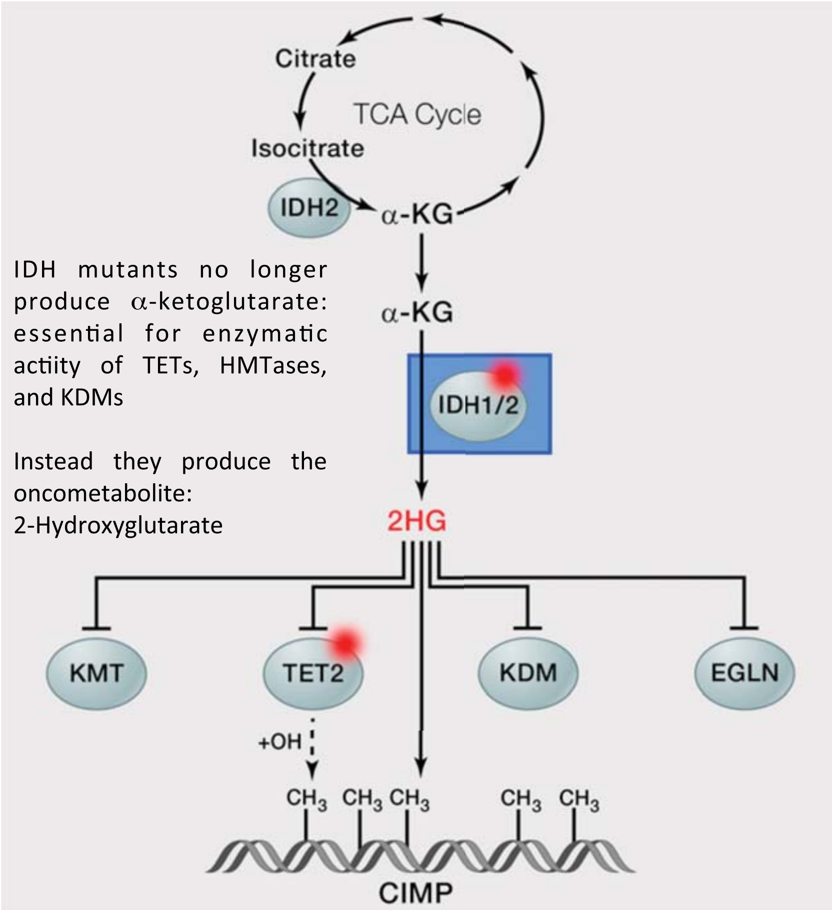
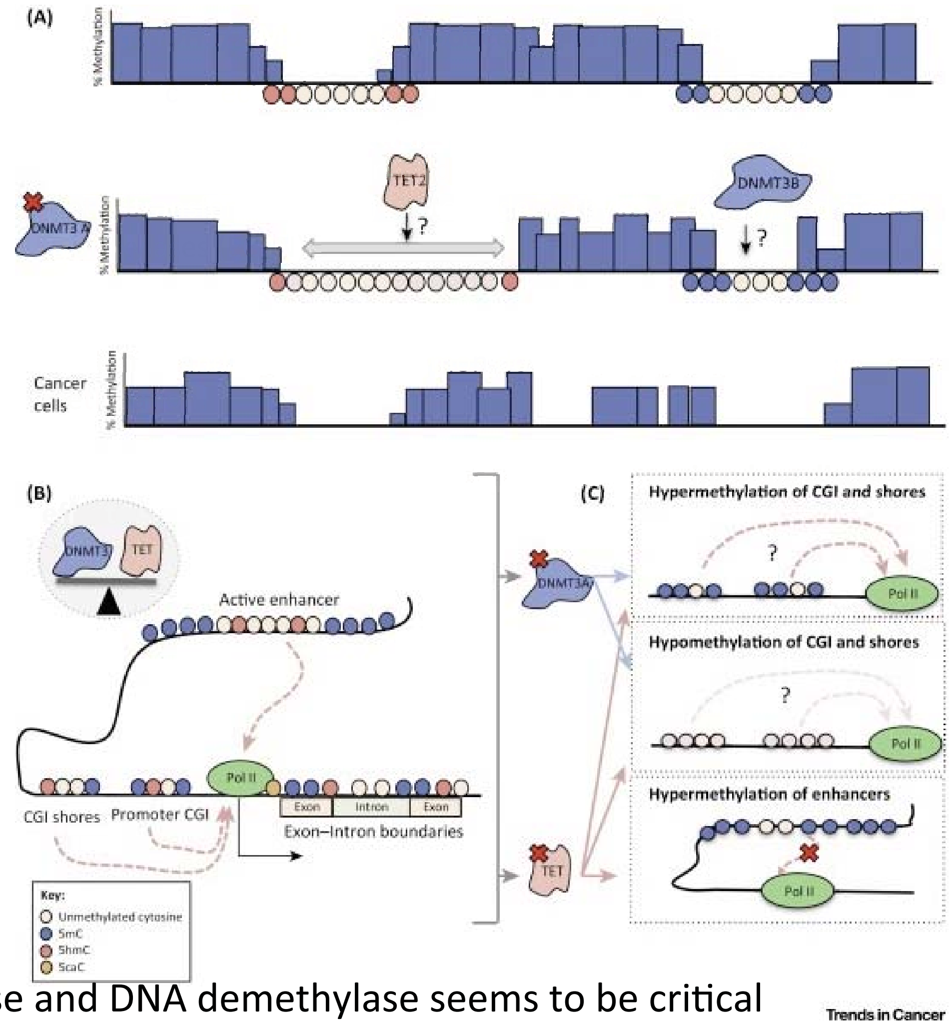
IDH1/2 mutations inhibit Tet2 (and other enzymes) and affect DNA demethylation





Balance of *de novo* DNA methyltransferase and DNA demethylase seems to be critical
Absence of either one leads to widespread changes in the epigenome, its overall organisation and at gene regulatory elements and repeats…

(More next week!)

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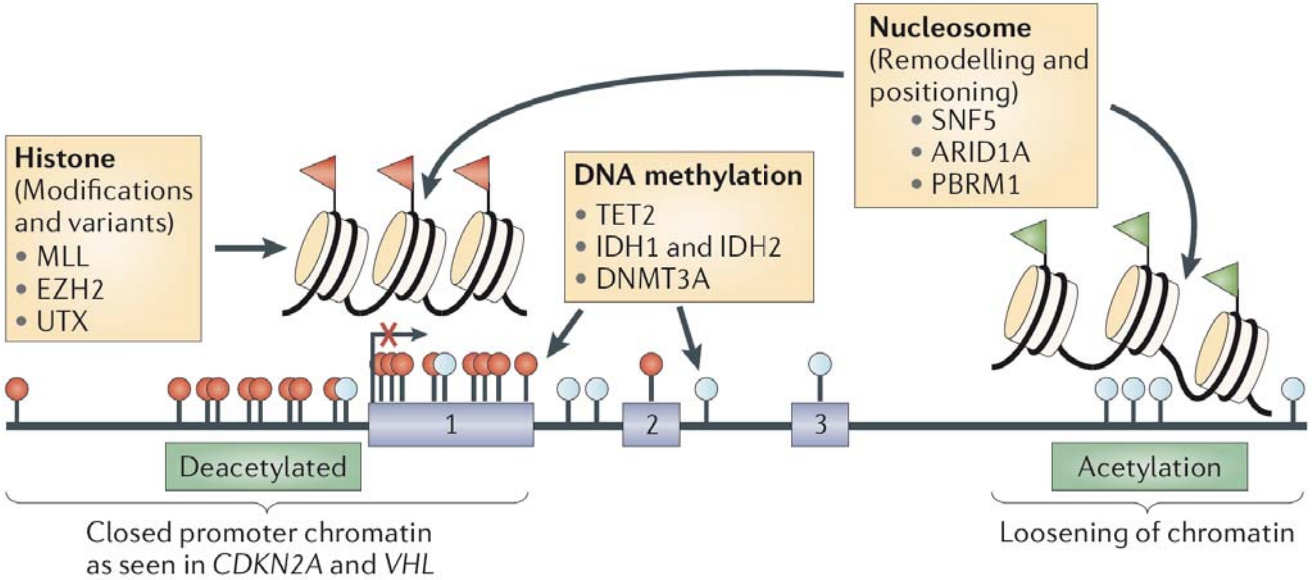
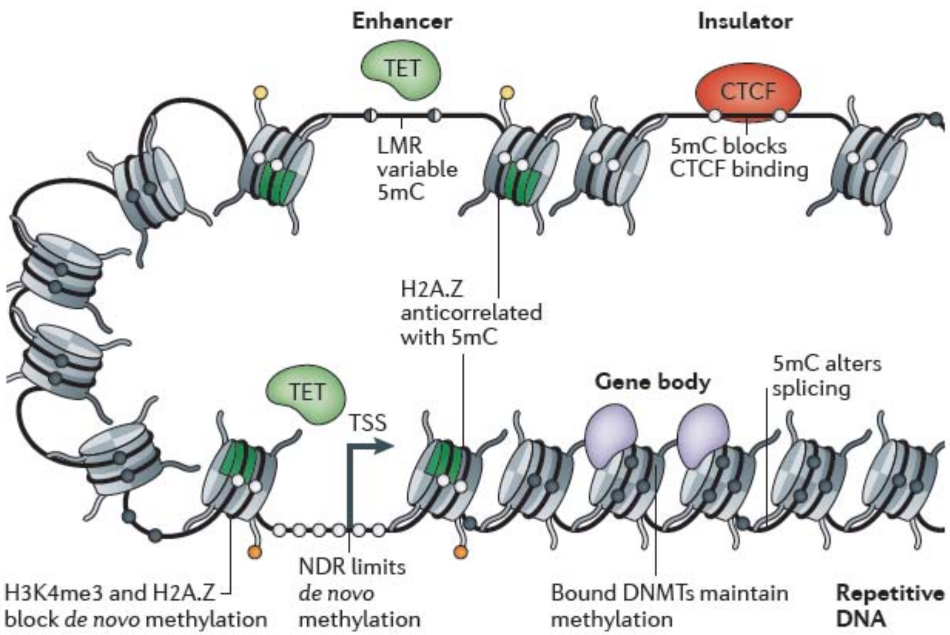
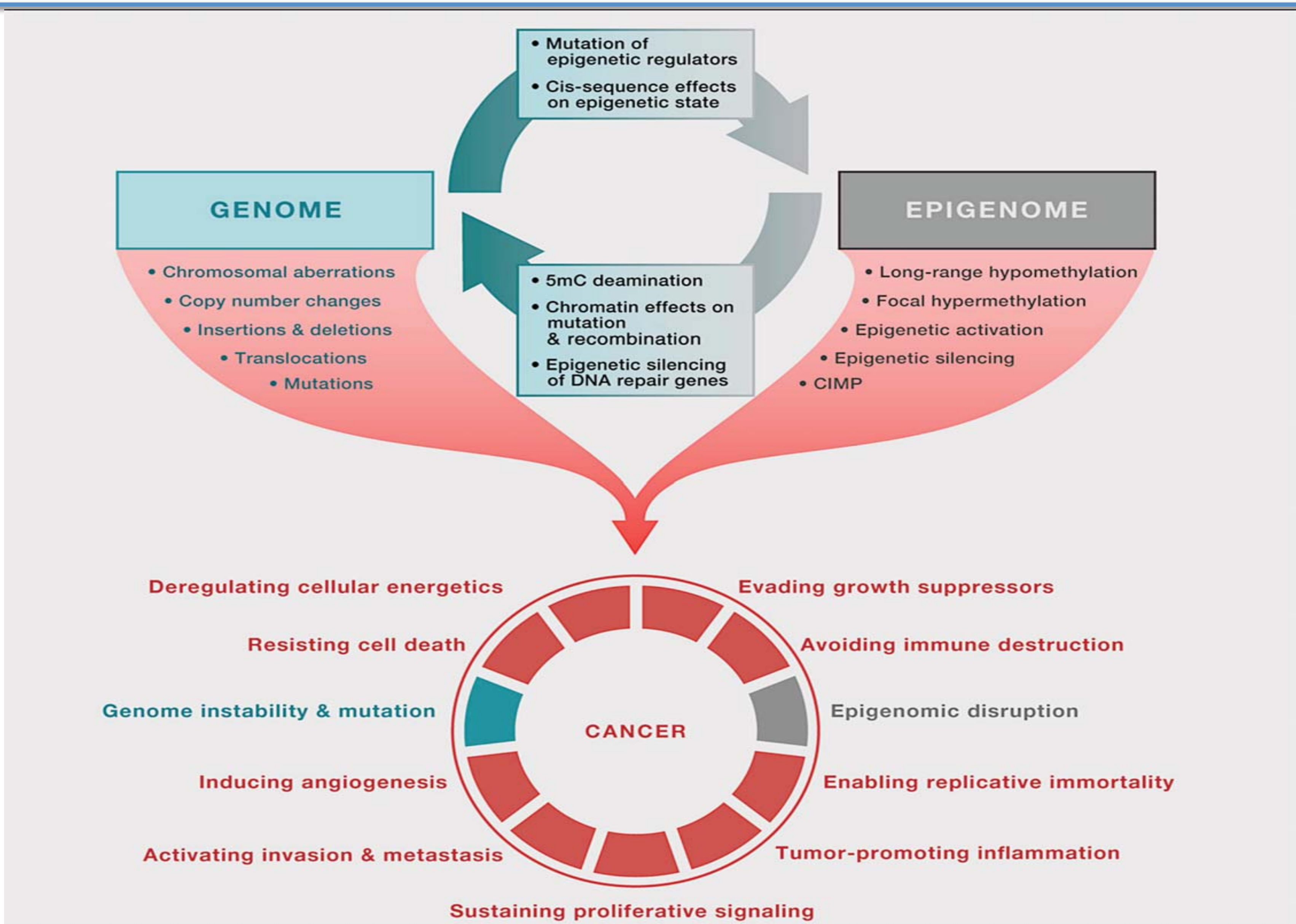
More Discoveries from Cancer Genomes



Bylin and Jones, 2011



Cancer genomes and the epigenomes



E. Heard, 2016

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CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2015-2016 :
"Epigénétique et Cancer"

14 mars, 2016

Cours III
"Contrôle épigénétique des gènes et des génomes dans le cancer »
"Epigenetic control of genes and genomes in cancer

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