CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2015-2016 :
"Epigénétique et Cancer"

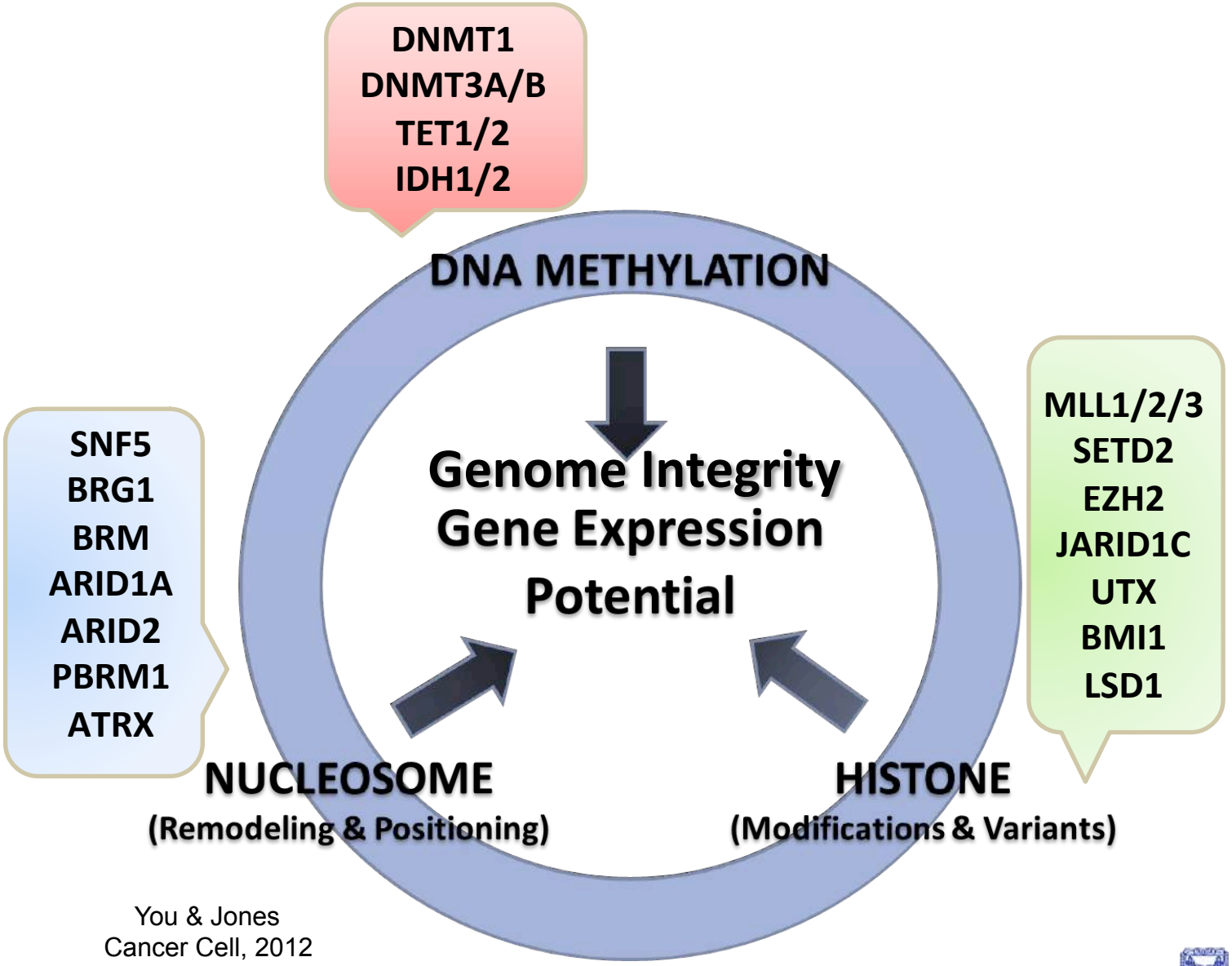
4 avril, 2016

Cours V

"**Voies épigénétiques du cancer II**"

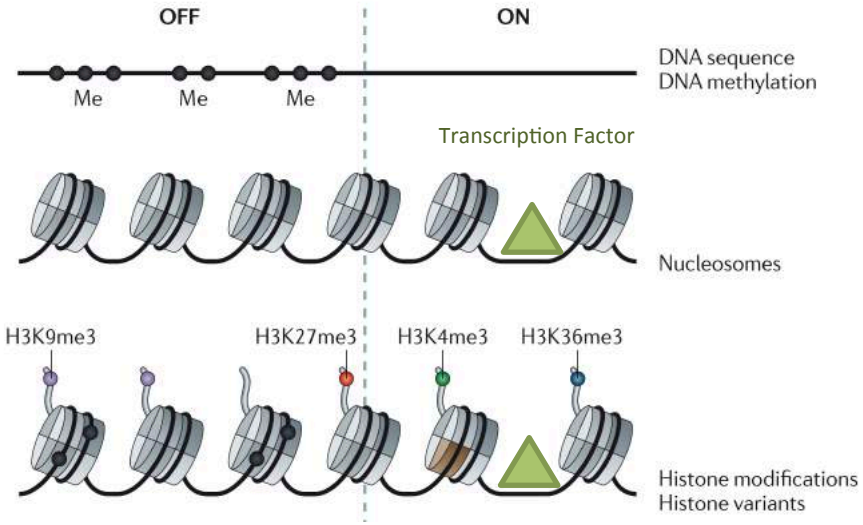
"*Epigenetic pathways in cancer II*"

Epigenetic Pathways in Cancer



You & Jones
Cancer Cell, 2012

Chromatin: the physiological template of the genome and a carrier of cellular memory



Epigenetic changes can be stably maintained yet adapt to changing developmental or environmental needs

- Chromatin acts as an epigenetic barrier: to prevent aberrant transcription
- Chromatin memory is progressively established during development
- Chromatin states have to be perpetuated during DNA replication/repair
- In cancer, chromatin states can be perturbed by redistribution of epigenetic regulators, their aberrant action or their loss
- Changes in epigenetic factors can have widespread effects on gene expression states, repeat silencing, genome stablity…multiple phenotypes

Mutated Cancer Genes affect a spectrum of Chromatin Modifers

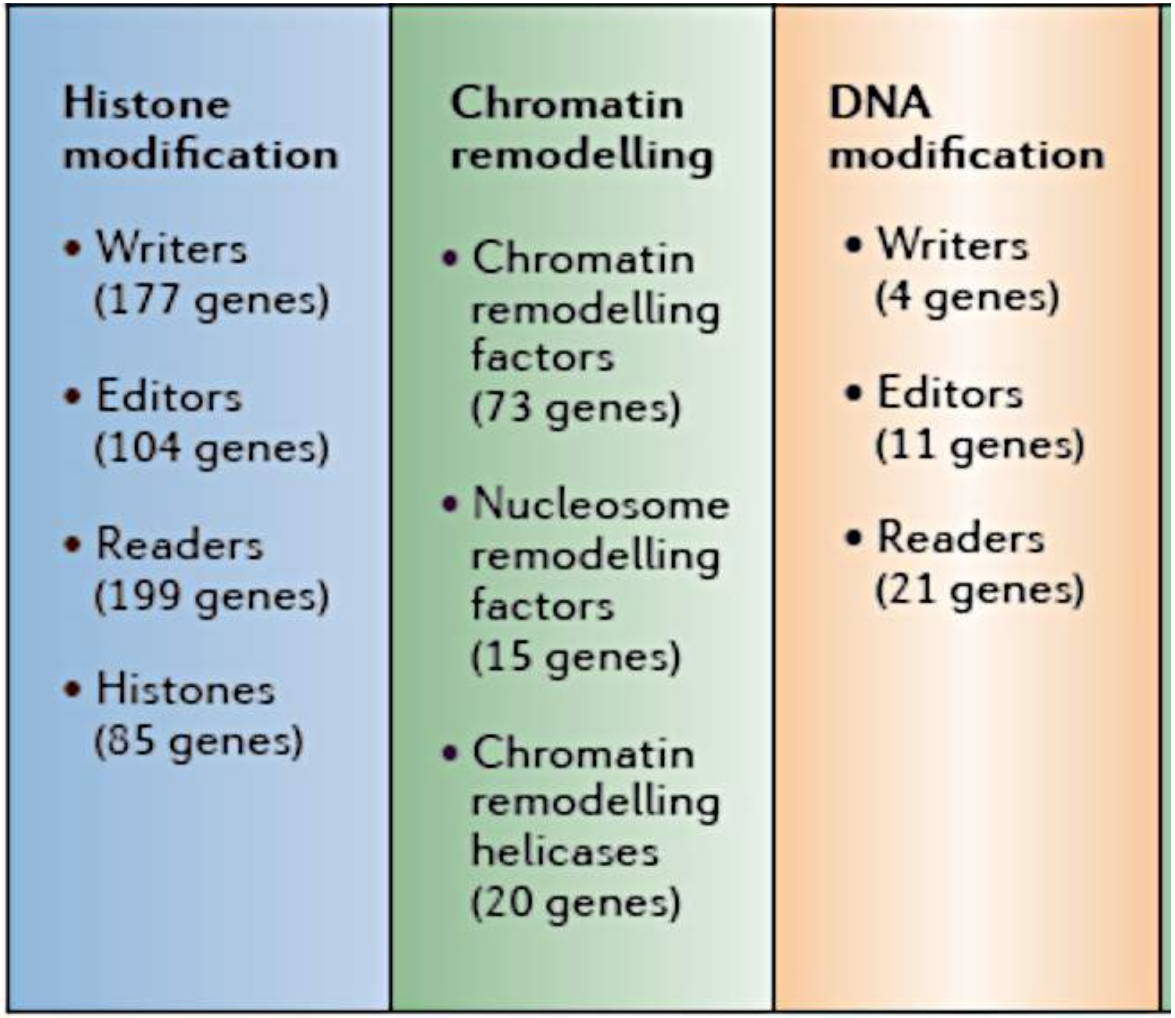
Cancer genomes/exomes have revealed alterations for numerous epigenetic proteins

Both gain and loss of function

Already useful for classifying specific tumors

Affected genes/cell functions still need to be understood…

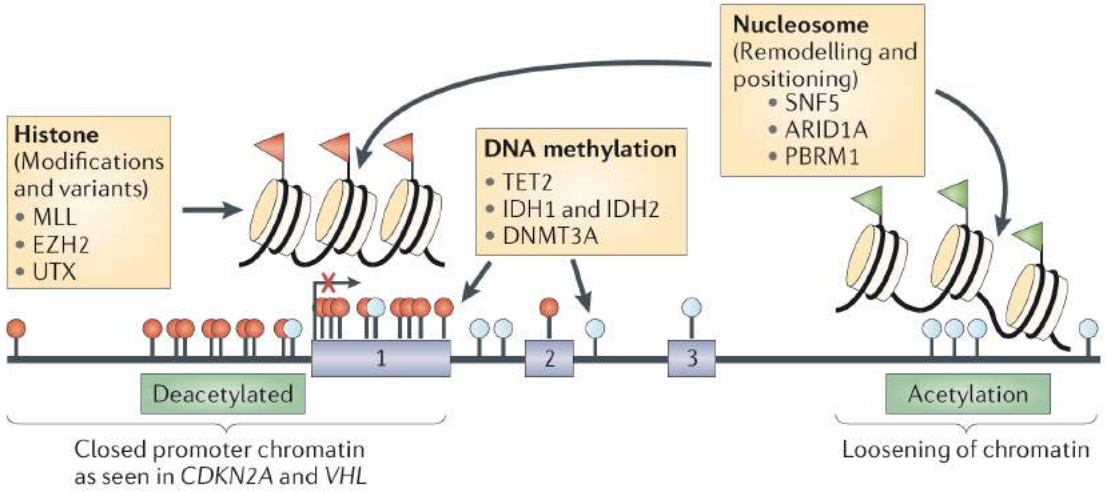
Targeted therapy already underway



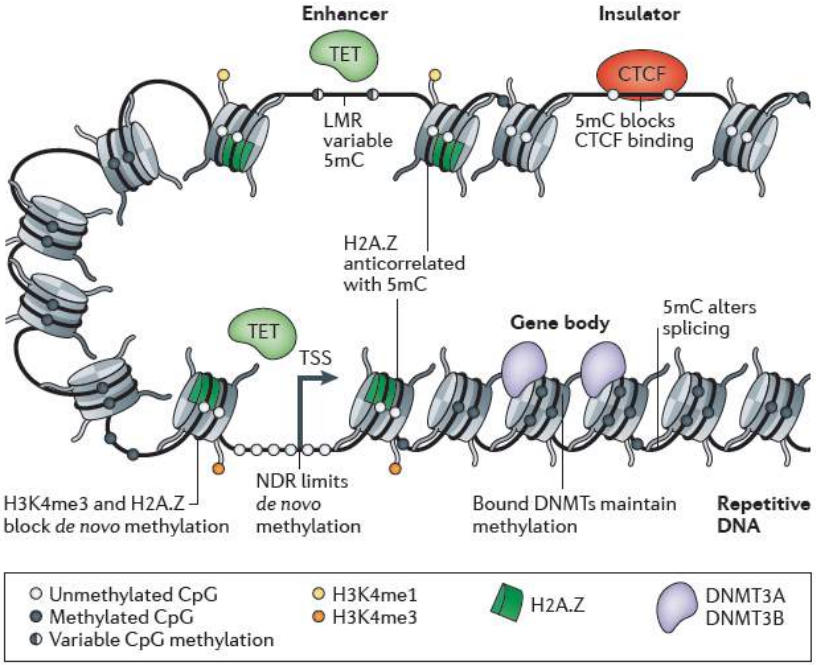
Shen et al, Cell 2013

Epigenetic modifers can act at many different levels

Genes



Regulatory Sequences



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Epigenetic modifers can act at many different levels

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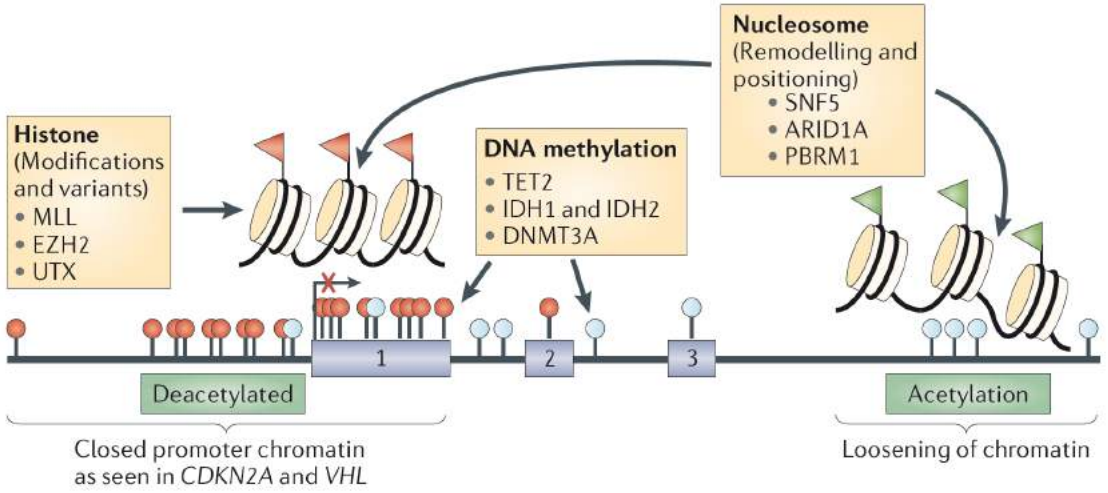
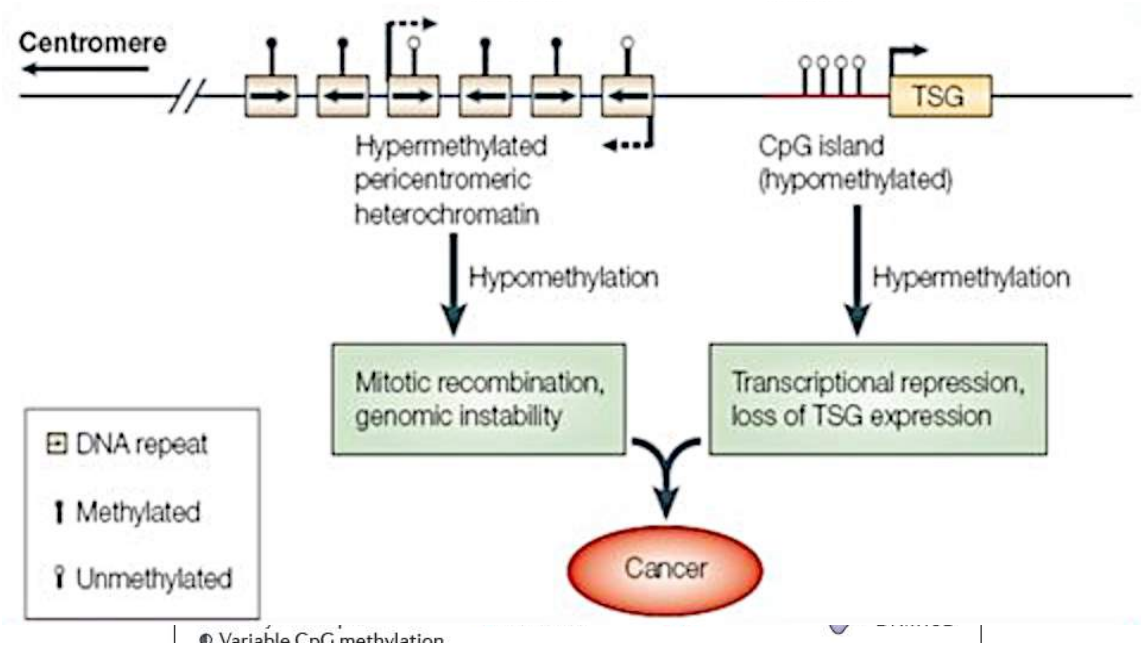


Repeats

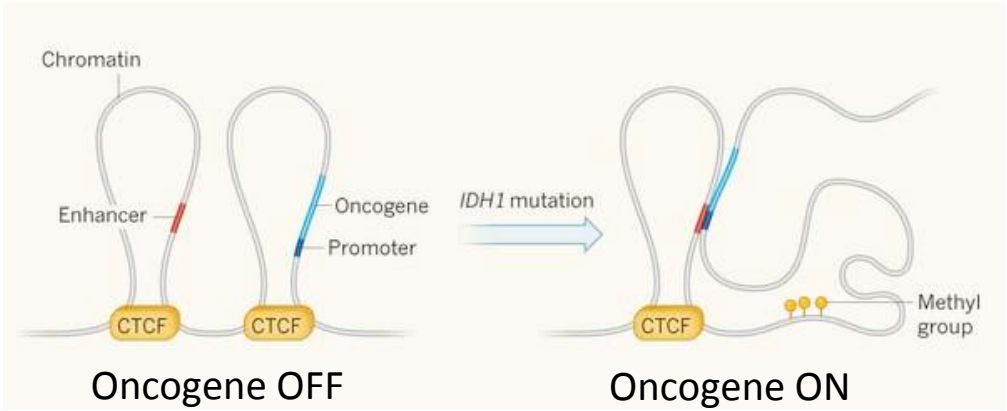


Summary of DNA methylation pathways

- **Mutations in DNA Methylation enzymes (DNMT3A, TET1/2 and IDH1/2) are frequent in some cancers (leukemia and lymphoma)**
- **Mouse models have demonstrated the direct role of these factors in tumor induction: Dnmt3a KO and Tet2/3 KO mice (increased HSC self renewal, myeloid skewing and transformation)**
- **Loss of Dnmt3a leads to *decreased* 5mC, while loss of Tet and IDH1/2 enzymes leads to *increased* 5mC; all mutants lead to *decreased* 5hmC**
- **Roles: Repeat control, gene regulation, enhancers, insulators, DNA repair…?**

Proposed model for impact of IDH mutations on oncogene activation:

- Gain of DNA methylation @ CpG sites including CTCF binding sequences
- Loss of CTCF binding – loss of insulation between regions
- Aberrant interaction between an enhancer (long range regulatory element) & promoter



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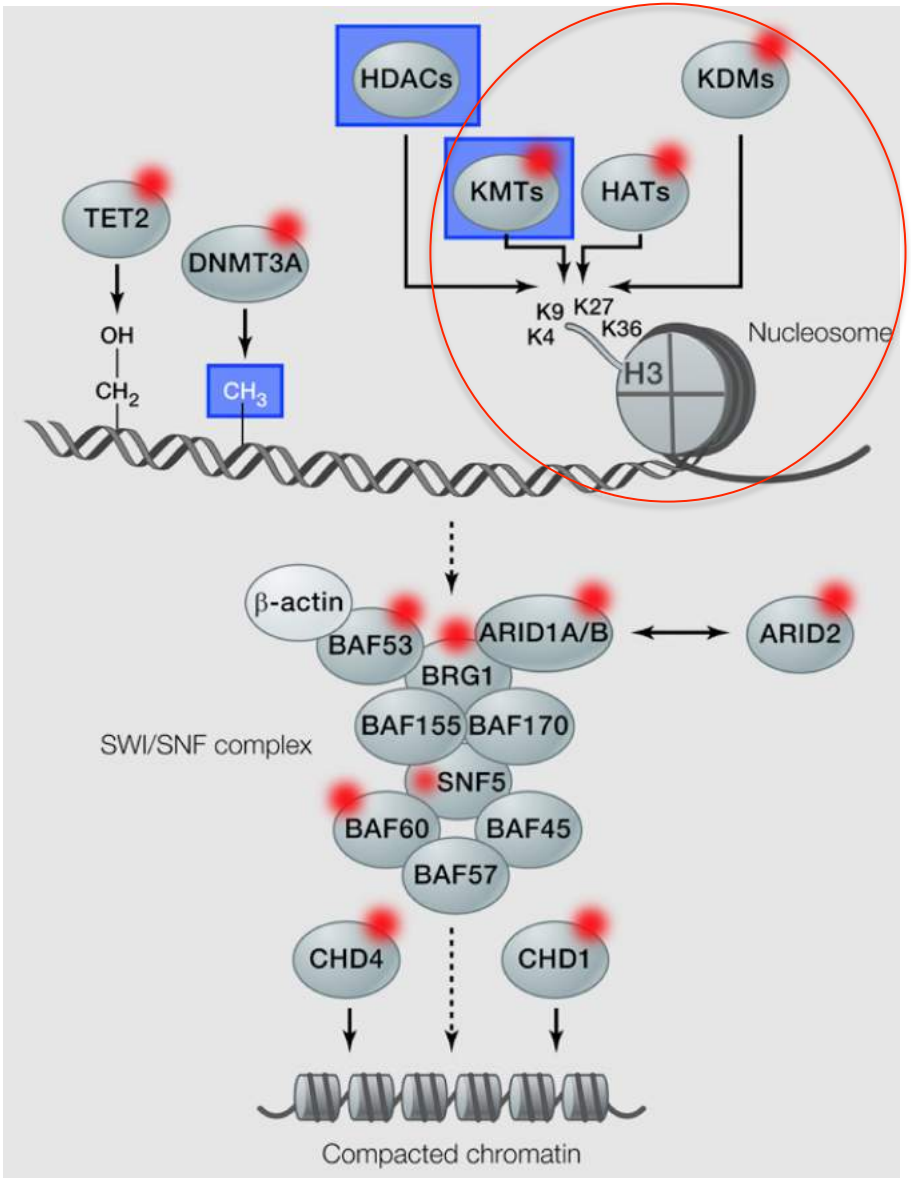
Whatever its functions,
aberrant DNA methylation can define tumor subtypes
⇒ Powerful prognostic value and important therapeutic target

Chromatin remodeling proteins, Histone Modifiers and DNA Methyltransferases/demethylases



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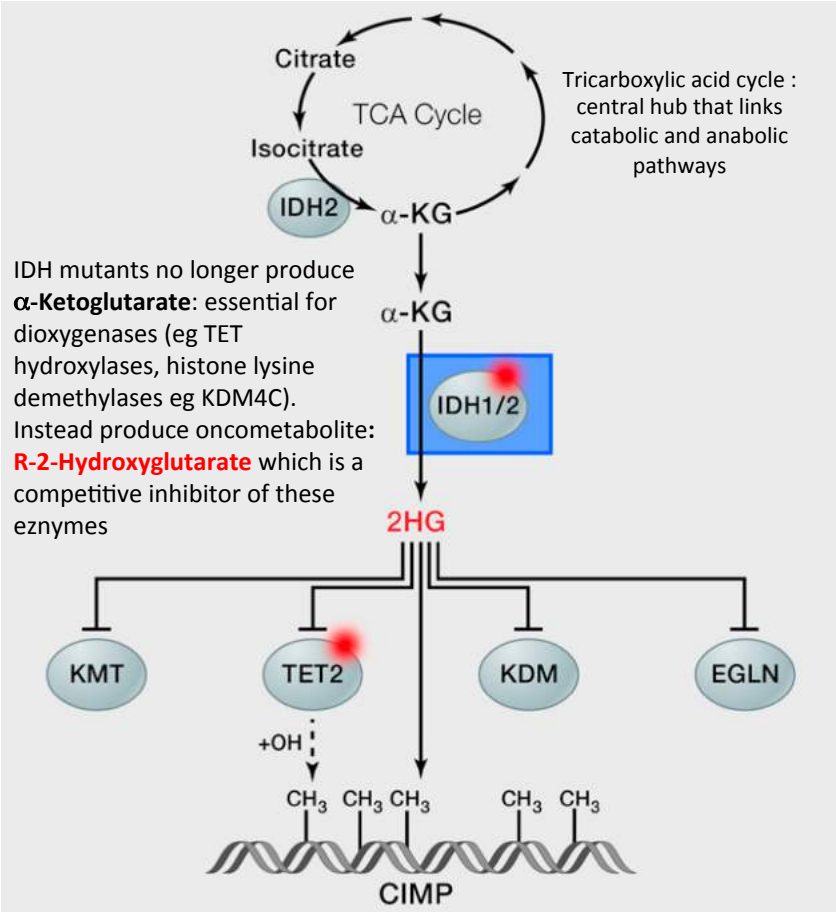
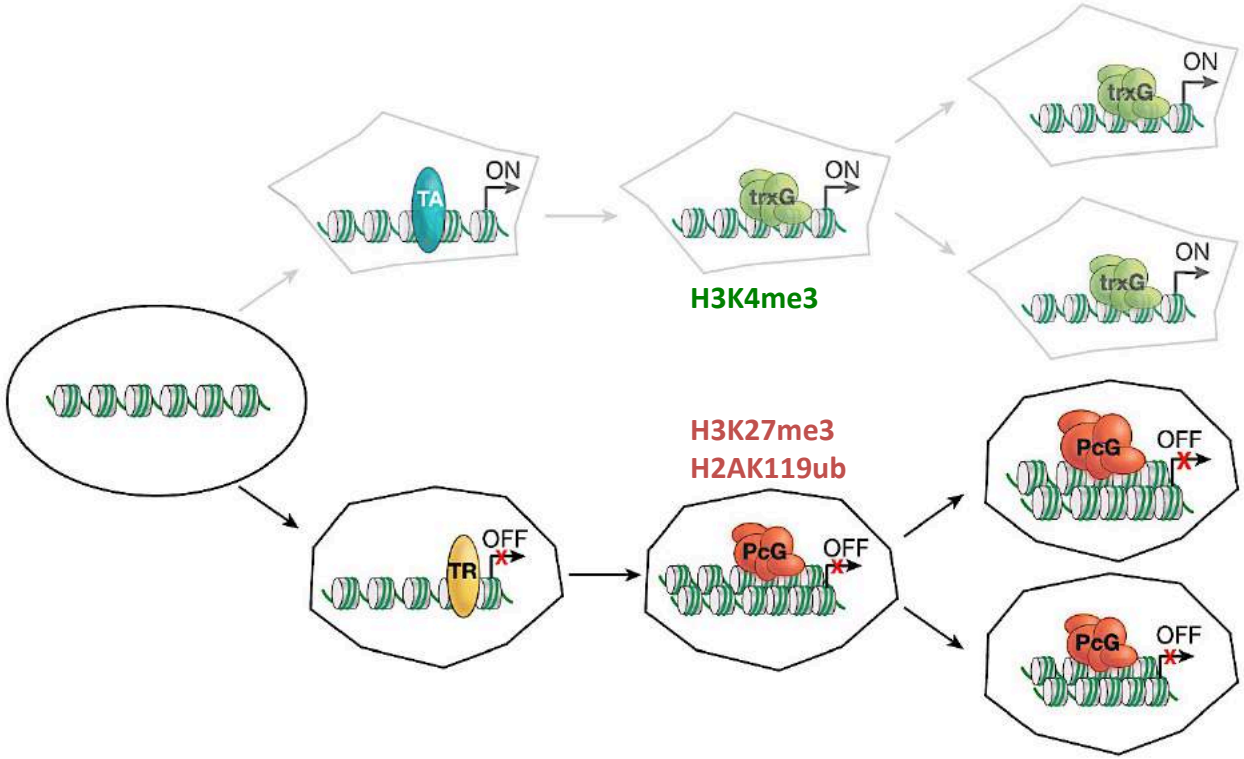


- IDH1 and IDH2 genes encode isocitrate dehydrogenases
- Mutations frequently found in many tumors (glioblastomas, leukemias)
- Gain-of-function IDH mutations: synthesis of 'oncometabolite' R-2-hydroxyglutarate (2HG) instead of α-ketoglutarate (αKG)
- 2HG is a competitive inhibitor of several α-KG-dependent dioxygenases (eg histone demethylase KDM4C, TET hydroxylases).

Dang, L. *et al.* Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* **462,** 739–744 (2009).

Polycomb and Trithorax Group Complexes

Active and inactive states of genes expression established by transcription factors are **maintained** during cellular differentiation by Polycomb (PcG) and trithorax (trxG) over multiple cell divisions



Maintenance of cell identity
Facultative heterochromatin
Stem cell plasticity
Bivalent states
(resolved into fully ON or OFF as development proceeds)

Disruption in development => homeotic transformations, germ line defects
Disruption in adults => stem cell defects, cancer…

Chromatin "memory" complexes that are more highly conserved than DNA methylation!

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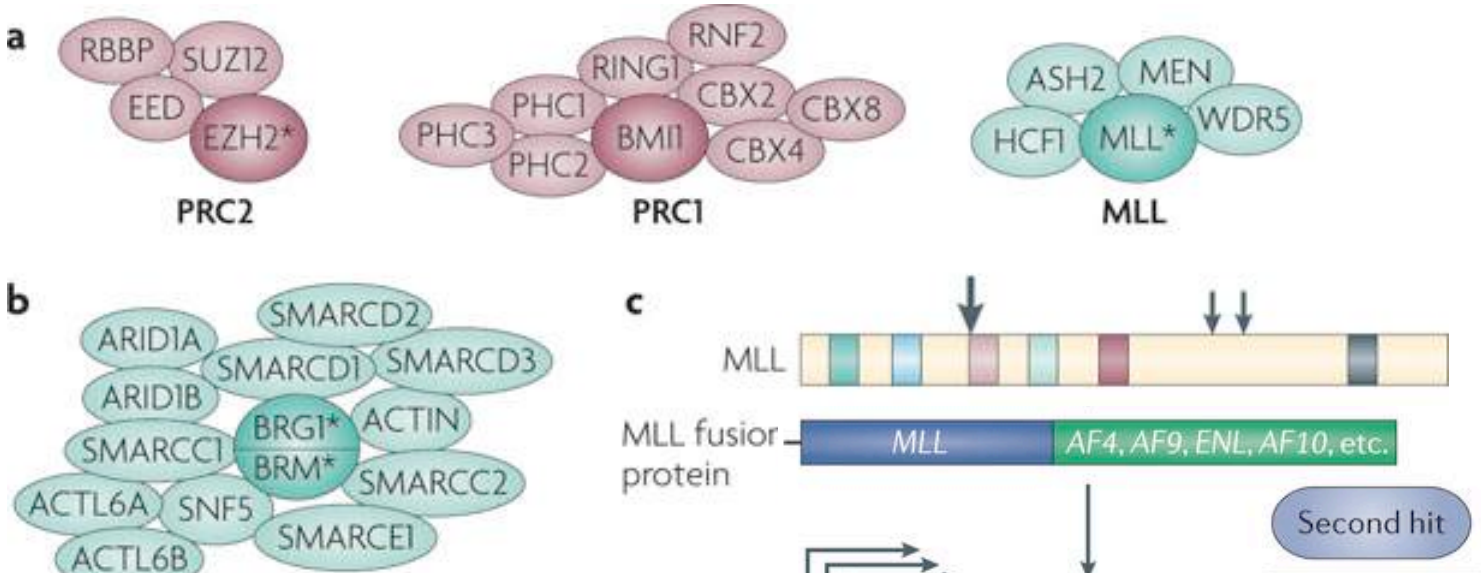
Polycomb and Trithorax Complexes in Cancer

Multi-protein complexes: core components including histone modifying enzymes plus subunits that can change during development and in different tissues

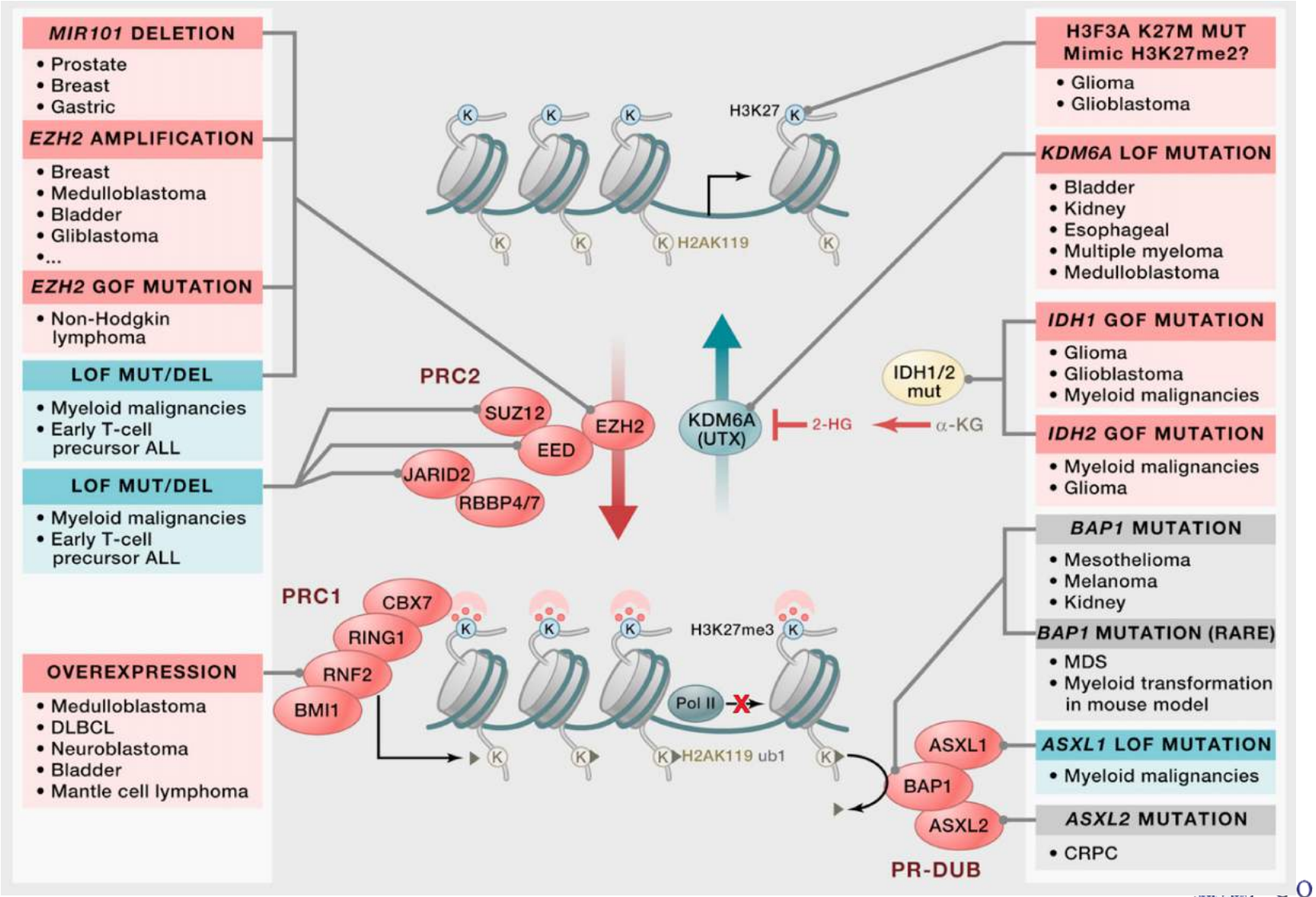


Altered TrX and PRC activities in cancer via:

- Fusions proteins (eg MLL)
- Mutations in some of these proteins or in their **targets** (eg histones)

Cancer

Genetic Disruption of Epigenetic Control at H3K27 in Cancer



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Shen and Laird, Cell 2013

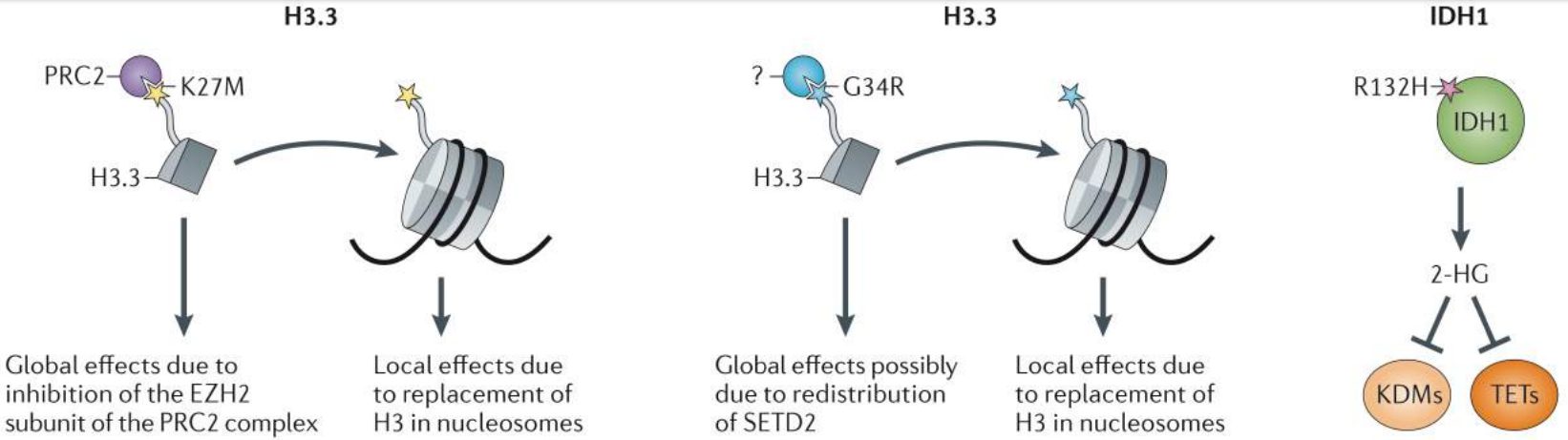
Paediatric and Adult Glioblastoma: Roles for Histone Variants, Chaperones and Modifying enzymes

- Glioblastomas are the most frequent and aggressive malignant primary brain tumors
- Brain tumors are the most common solid tumors in children.
- Pediatric high-grade glioma (HGG) accounts for 8– 12 % of brain tumors
- Devastating disease as 70–90% of patients die within 2 years of diagnosis
- Failure to treat children over last 30 years : largely due to limited knowledge of the molecular basis for these tumors + a lack of disease models.
- Recent sequencing of tumors revealed recurrent combinations of genomic and/or epigenetic aberrations associated with glioblastoma: meaningful subgroup classifications
- Found genetic lesions disrupting several epigenetic controllers at high frequency
- Remarkably, the histone H3 variants H3.1 and H3.3 are frequently mutated in pediatric HGG, with up to 78 % of diffuse intrinsic pontine gliomas (DIPGs) carrying K27M and 36 % of nonbrainstem gliomas carrying either K27M or G34R/V mutations.

=> First demonstration that histone mutations may be drivers of disease.

- High-frequency mutation of histone H3 to K36M found in chondroblastomas and to G34W/L in giant cell tumors of bone, which are diseases of adolescents and young adults.
- Intriguingly, Histone H3K27M mutations very rare in older patients

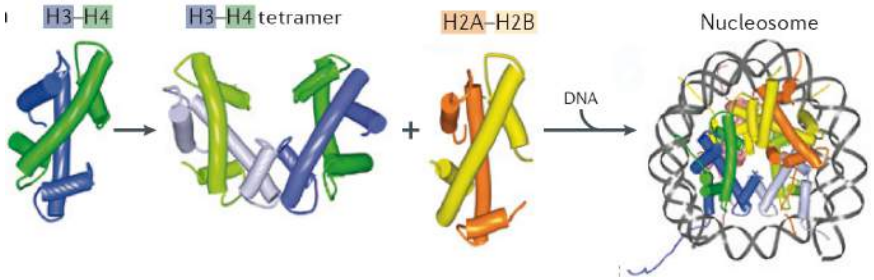
Paediatric and Adult Glioblastoma: Roles for Histone Variants, Chaperones and Modifying enzymes



	H3.3-K27M mutation	H3.3-G34R mutation	IDH1-R132H mutation
Targeted enzyme	EZH2 in PRC2	SETD2?	KDMs and TETs
5mC	Hypomethylation	Hypomethylation	Hypermethylation
Histone modifications	H3K27me3 decreased and redistributed	H3K36me3 redistributed	H3K9me3 increased, H3K27me3 increased, H3K4me3 increased and H3K36me3 increased
Developmental gene-expression pattern	Neurogenic and mid-to-late cortical development	Neurogenic and early-to-late neocortical development	Neurogenic and neural progenitor cell bias
Gene expression owing to 5mC changes	PRC2-target genes upregulated, *FOXG1* downregulated and *OLIG2* upregulated	*MYCN* upregulated, *FOXG1* upregulated and *OLIG2* downregulated	Genes involved in differentiation downregulated
ALT	Yes	Yes	Not known
Prevalence in childhood glioblastoma	19%	15%	<10%
Prevalence in adult glioblastoma	0%	0%	77%

Specific Histone Variants & Cancer

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

Gain of function mutations in H3.3 K27M, H3.3 G34E and G34V leads to very specific gliomas.

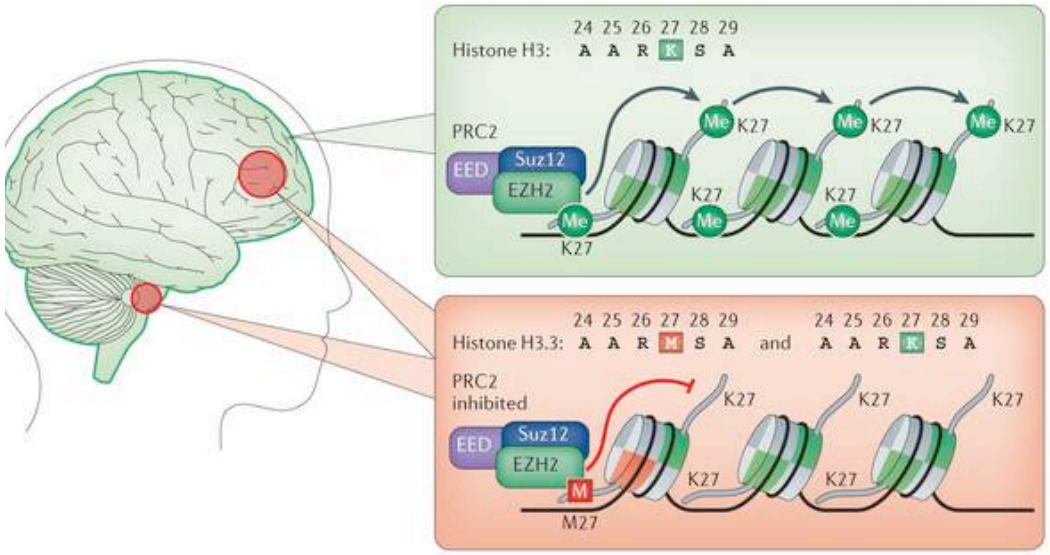
Mutations always heterozygous, even though >10 different H3 genes (H3.1, H3.2, and H3.3) in humans.

G34R/V mainly leads to the redistribution of H3K36me3, possibly by redirecting its enzyme SETD2 - leading to enhanced expression of eg *MYCN*?

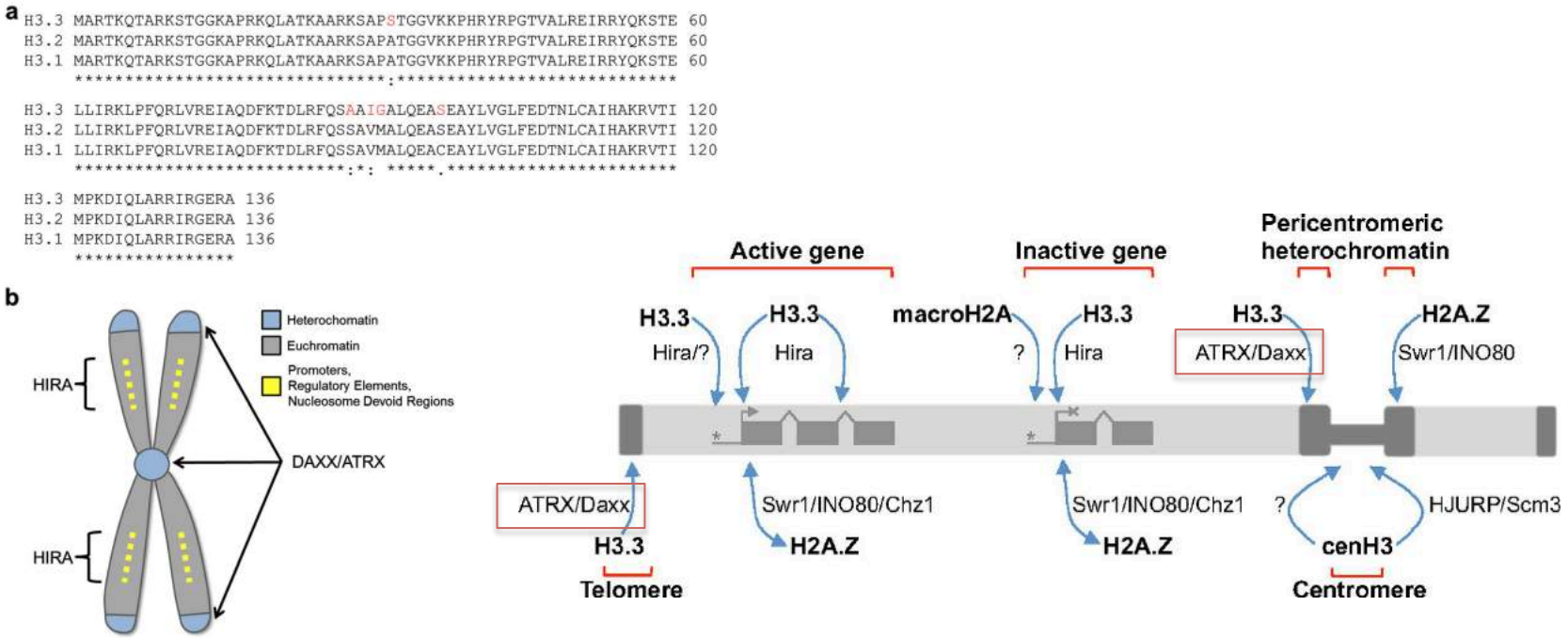
H3K27M interferes with PRC2-EZH2 activity leading to global down regulation of H3K27me3

Reprogramming of epigenetic landscapes:

- genome wide loss in H3K27me3
- specific (aberrant) enrichment of the mark at several hundred genes.
- global DNA hypomethylation



Specific Histone Variants & Cancer



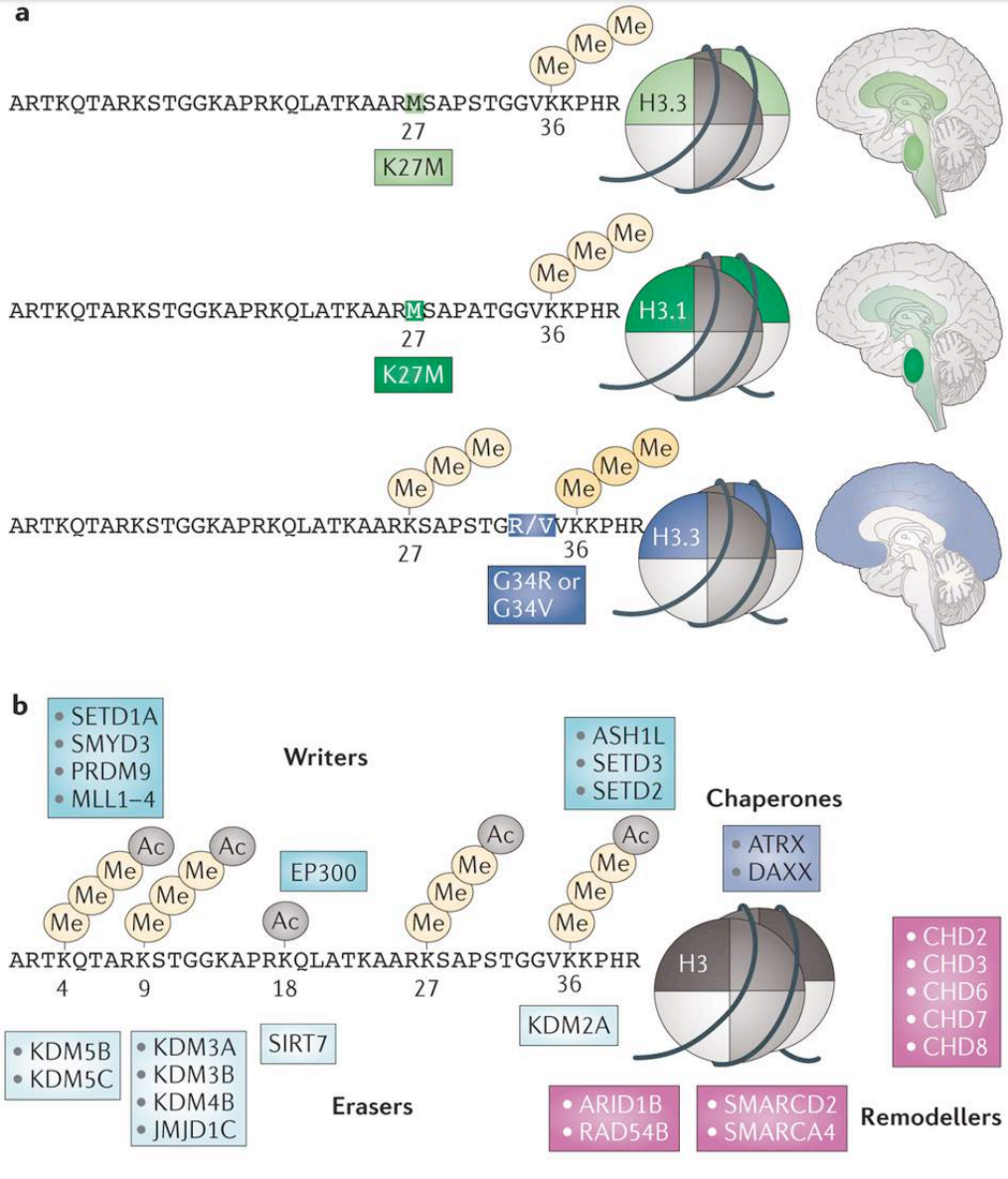
H3.1 is deposited during DNA Replication - S phase

H3.3 has been noted at promoters and bodies of transcriptionally active genes, promoters of silent genes, enhancers, and pericentromeric and telomeric regions (Skene and Henikoff, 2013).

Mutations in the **DAXX** (death domain-associated protein)/**ATRX** (alpha thalassemia/mental retardation syndrome X-linked protein) **chaperone complex** that loads H3.3 at pericentromeric and telomeric regions are associated with alternative lengthening of telomeres (ALT)

H3.3-G34R/V mutation showed a 100% overlap with ATRX-DAXX mutations, unlike the H3.3-K27M mutation

Unique genetic and epigenetic mechanisms driving paediatric diffuse high-grade glioma



Jones and Baker, NRC, 2014

Nature Reviews | Cancer

Glioblastomas are very heterogeneous:

- Different tumor locations
- Patient ages
- Mutational spectra
- Neuronal lineage markers

Speculate that some GBM subgroups may have a unique cellular origin?

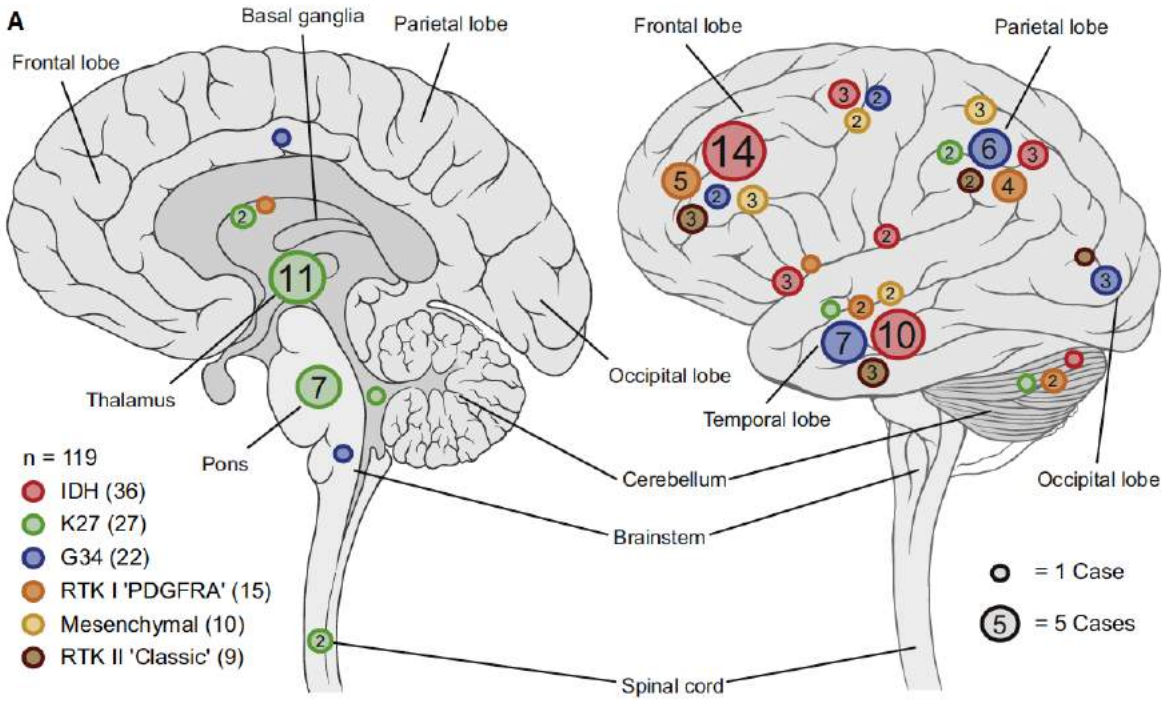
GBM are highly heterogeneous both between and within tumors:

Single cell RNA profiling reveals diverse transcriptional programs – related to cell proliferation, oncogenic signaling, hypoxia, complement/immune response – and a continuum of "stemness"-like expression states (Patel et al, Science 2014)

GBMs contain cellular niches enriched for distinct phenotypic properties such as transient quiescence.

Better classification of tumors required: genome, transcriptome, epigenome…

Hotspot Mutation in H3.3 and IDH1 define Distinct Epigenetic and Biological Subgroups of Glioblastoma



- GBM can now be sub-classified into multiple molecular groups that are <u>indistinguishable by histological appearance</u>
- 6 GBM subgroups displaying characteristic global DNA meth patterns, with distinct hotspot mutations, SNVs and transcription patterns
- Hope that these classifications will help in diagnosis and treatment of this most common and most devastating brain tumor (5-year survival rate <10%)

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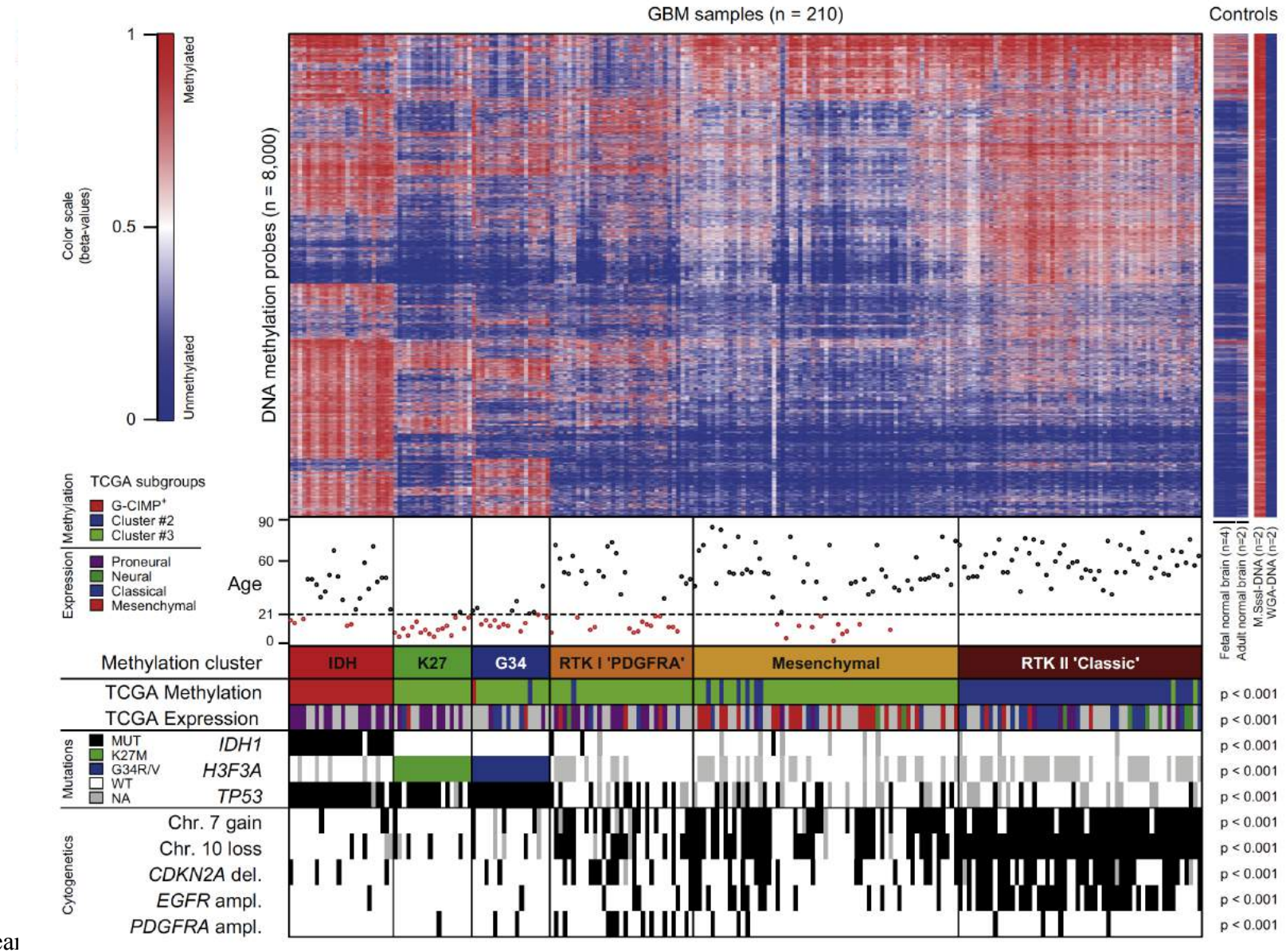
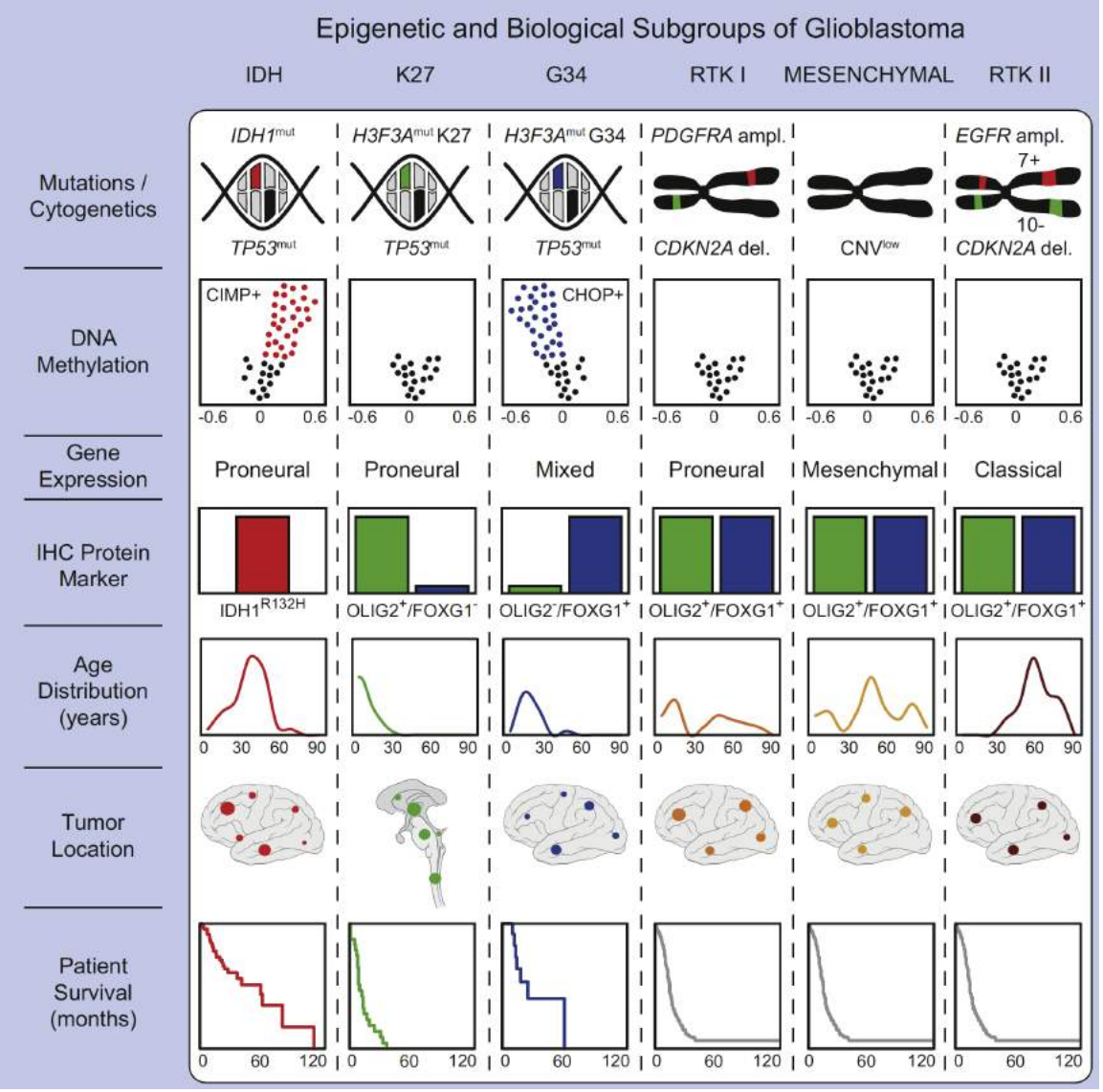


E. Hea

Hotspot Mutation in H3.3 and IDH1 define Distinct Epigenetic and Biological Subgroups of Glioblastoma



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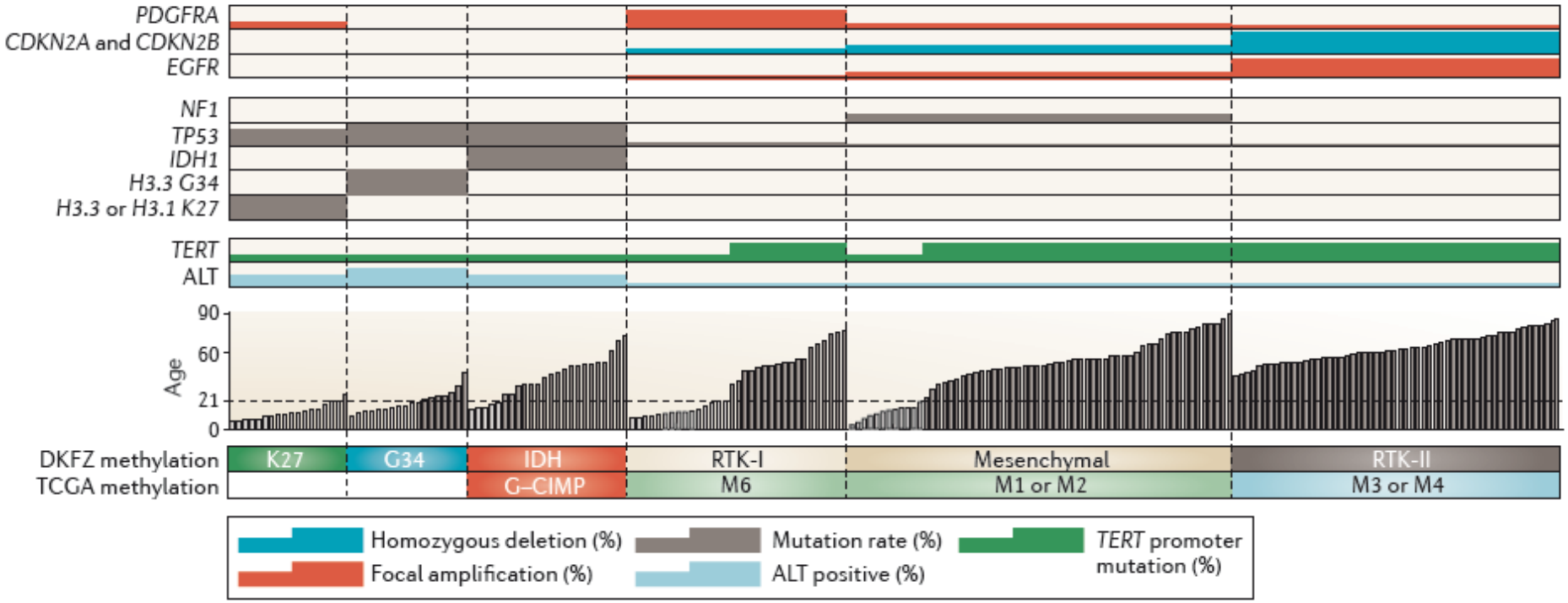
Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma



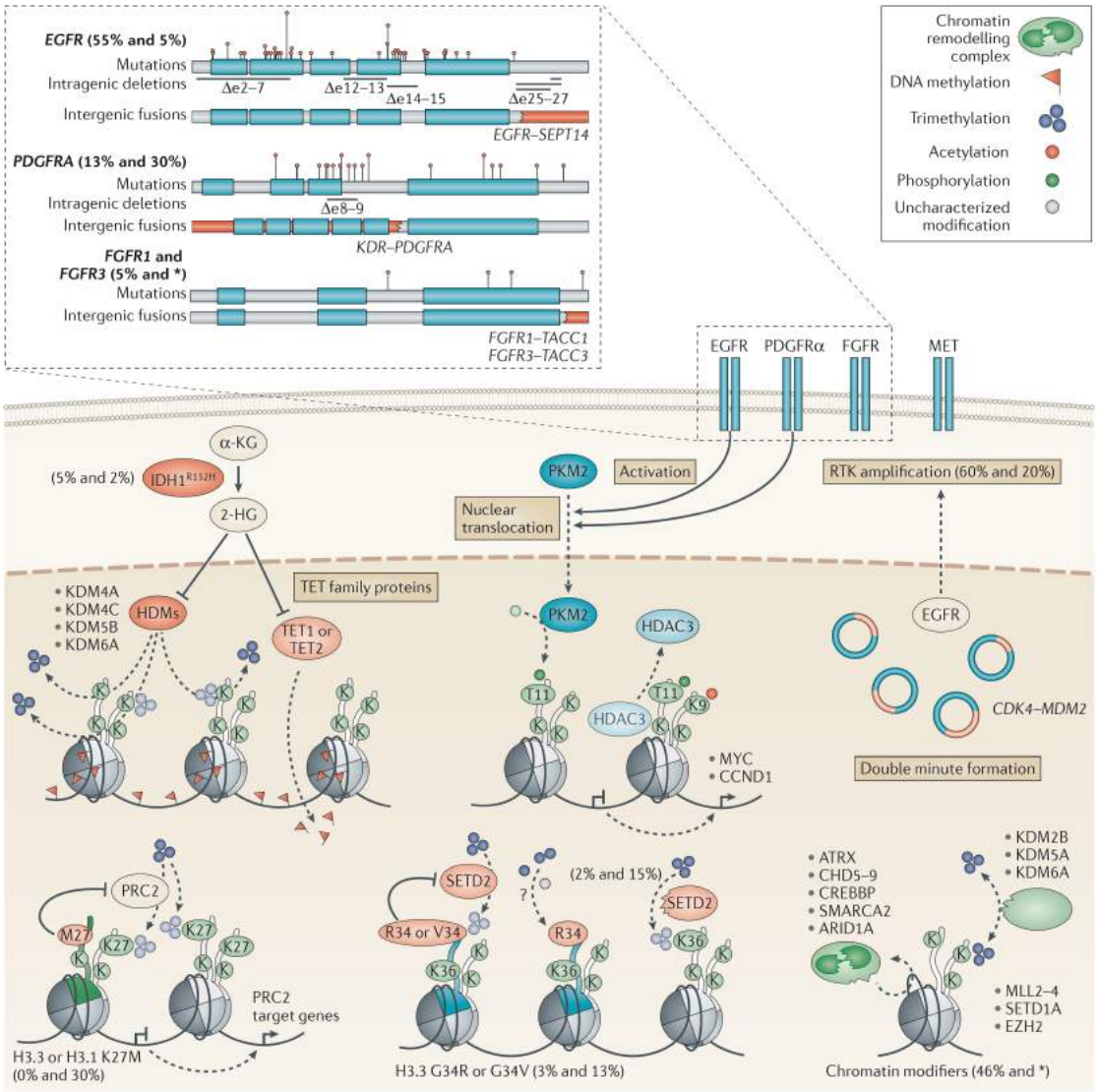
The realisation that epigenetic alterations play an important role in gliomagenesis, combined with the rapid development of drugs targeting epigenetic modifiers offers opportunities for innovative targeted approaches.

Understanding the mechanisms by which these alterations lead to cancer will be critical for optimal treatment however…

Sturm et al, Nat. Rev. Cancer, 2015

Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma

Pediatric (left) + adult(right) glioblastoma mutation %



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Modeling pediatric gliomas with H3.3K27M histone mutations

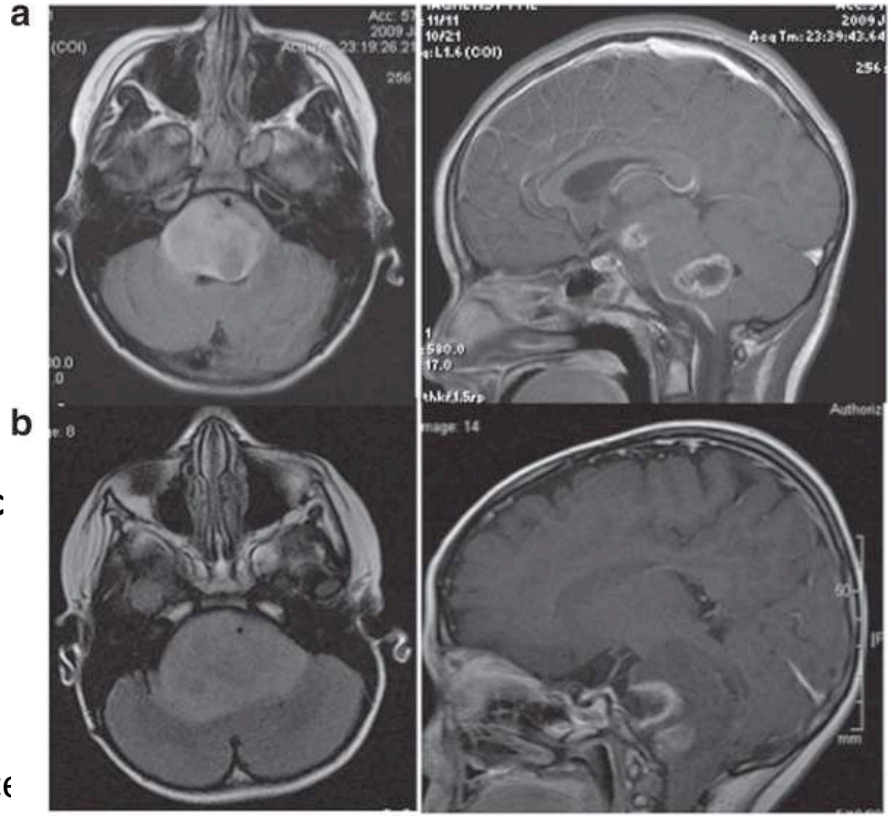
Use of human embryonic stem cells to model pediatric gliomas with H3.3K27M histone mutation. Funato, Major, Lewis, Allis, Tabar (2014) Science, 346, 1529

• Poor prognosis, untreatable diffuse intrinsic pontine gliomas (*tumeur du tronc cérébral*)
>70% are mutated for H3F3A

• Located in a highly sensitive part of the tumor in the brainstem : difficult to access

• K27M-mutated DIPGs occur during a restricted developmental window [mean age at diagnosis is 8 years] and have a specific midline location:
⇒ **developmentally early and anatomically specific cell of origin?**

• Genomics/epigenomics studies :
H3.3K27Mmutation identifies a distinct subgroup of DIPGs - overlap with p53 mutations & platelet-derived growth factor receptor (PDGFRA - cell surface tyrosine kinase receptor) amplification (60% and 40%, respectively).



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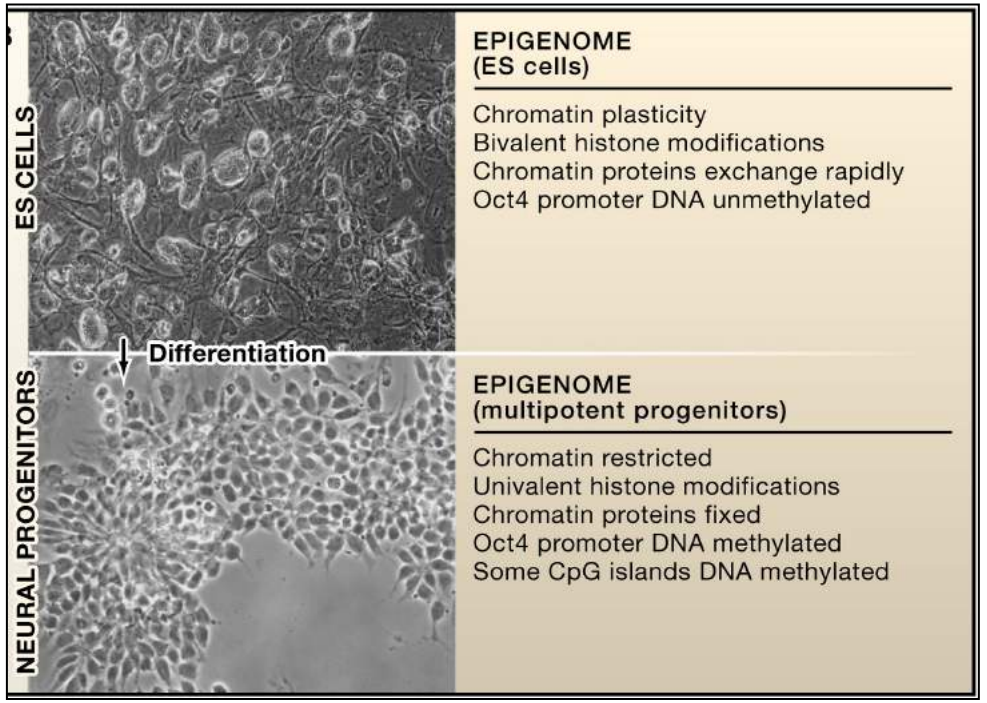
- Introduction of H3.3K27M into p53-null, nestin expressing progenitors in the neonatal mouse brainstem is insufficient to generate gliomas (Lewis et al, 2013) => glioblastomas must require additional mutations to form?

- Use **human pluripotent stem cells** (hPSCs) as a model for studying DIPG:

⇒ **functional analysis of oncogenic mutations in a genetically defined human background**

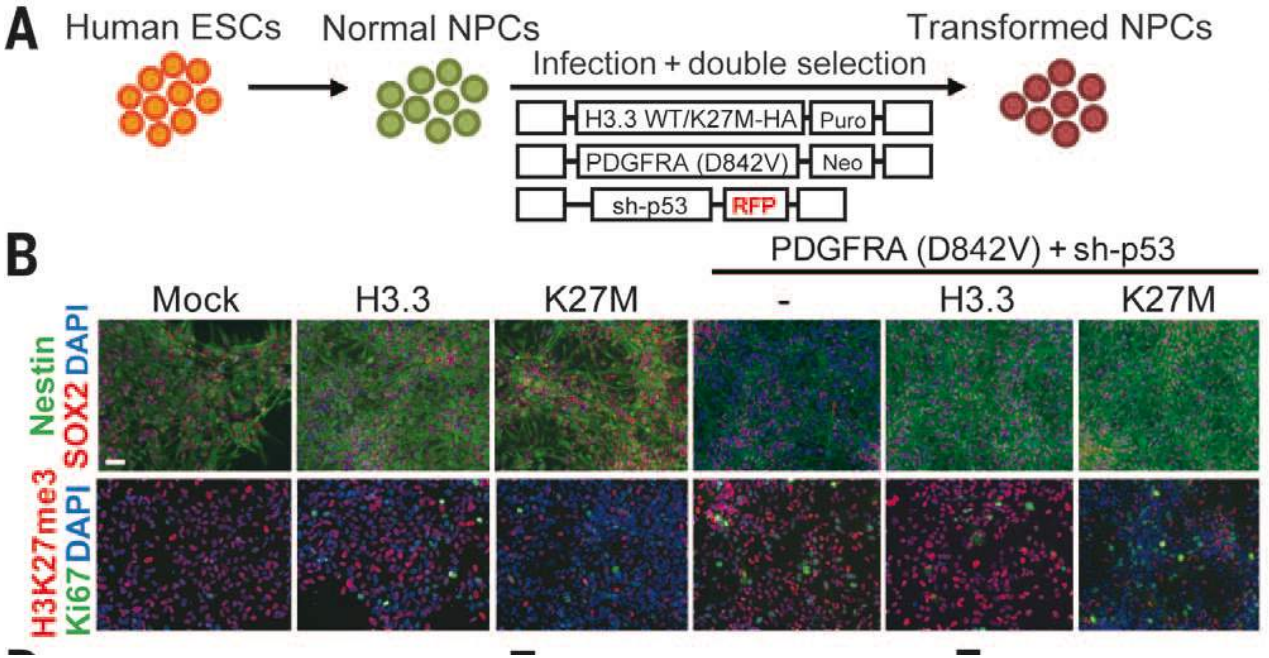
- Derive early neural progenitor cells (NPCs) from human ESCs and co-transduce (lentiviral infection) a constitutively active form of PDGFRA, a shRNA against p53 and a HA-tagged H3.3K27 mutant (based on high frequency in DIPGs)



Modeling pediatric gliomas with H3.3K27M histone mutations

- Expression of H3.3K27M led to a reduction in histone H3K27 trimethylation
- Expression of H3.3K27M, or overexpression of PDGFRA, or p53 KD all show increased NPC proliferation
- All three give >30% increase proliferation (Ki-67) and a synergistic effect on cell survival
- After growth factor withdrawal: >> apoptotic cells in H3.3K27M-expressing cells compared to normal

⇒ proliferative effect is balanced with increased apopototic rate – as often seen in pre-malignant states



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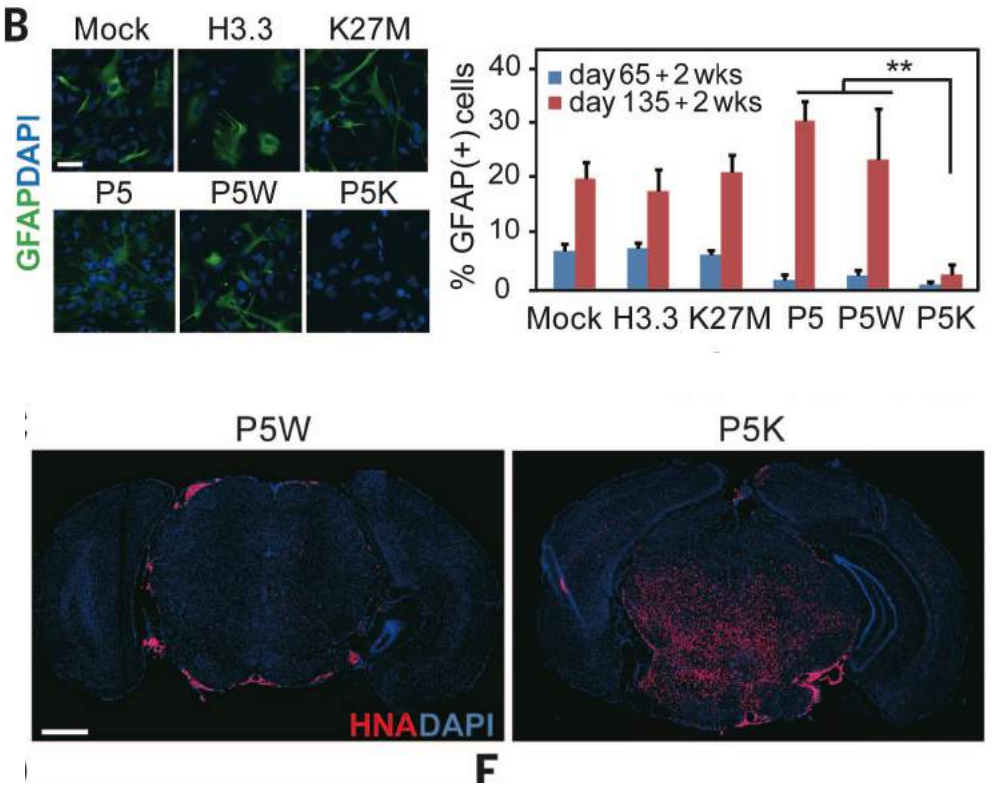
Modeling pediatric gliomas with H3.3K27M histone mutations

- Near-complete differentiation block in astrocytic lineage in the P5K cells
- Transcranial injection of P5K cells into the brainstem of mice led to slow but massive tumor formation
- Pathologically, tumors resemble lower-grade DIPGs rather than full-blown glioblastomas (GBMs)
- Transcriptomes: tumors comparable to patient DIPGs with H3K27M (not H3G34R/V) mutations
- K27M-expressing tumor cells express subset of transcripts found in neuroepithelial cells at a very early developmental stage—neural plate, which precedes the emergence of NPCs.



Expression of mutant H3.3K27M leads to a developmental resetting of neural precursors to a more primitive stem cell state, which in combination with growth factor signaling, results in the acquisition or consolidation of oncogenic features.

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Modeling pediatric gliomas with H3.3K27M histone mutations

H3.3K27M introduced into human neural progenitor cells and combined with PDGFRA activation and p53 loss, leads to tumor formation in xenotransplants

• **Driver role** for H3.3K27M mutation in gliobastoma in the appropriate cell context and developmental window

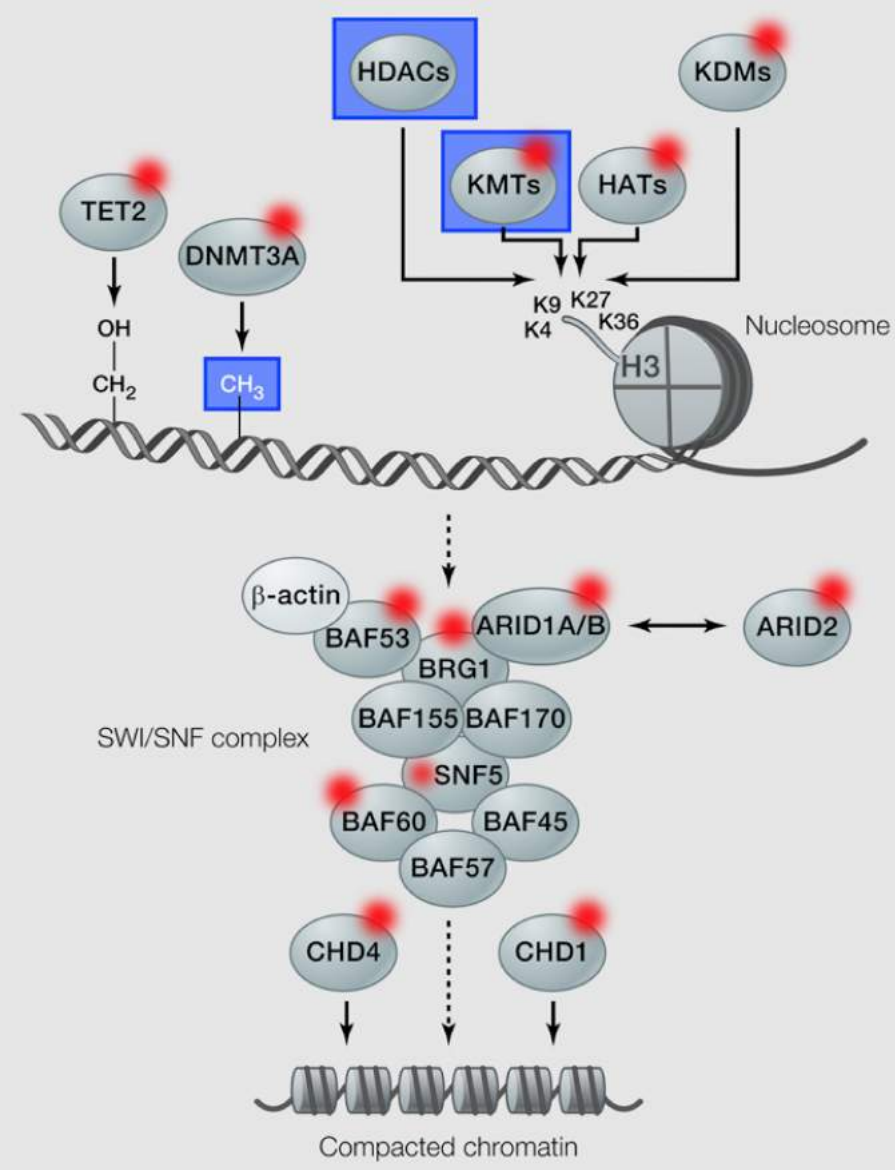
• Altered chromatin landscape induced by H3K27M facilitates the **reacquisition of an earlier developmental program** with subsequent **activation of factors crucial to reprogramming and oncogenesis** eg miRNA binding protein LIN28B

• A chemical screen identified the **menin pathway** as a contributor to tumor maintenance. Menin is a tumor suppressor (mutated in patients with an inherited syndrome, multiple endocrine neoplasia type 1). MENIN interacts with histone H3 methyltransferases such as MLL to alter their activity.

• Menin inhibitor (MI-2) significantly reduced K27M-expressing cell survival and tumor growth in this model. Potential opportunity for therapeutic intervention.

• Another study revealed that inhibition of JMJD3 has robust antitumor activity in diffuse intrinsic pontine glioma xenografts. **(COURS VI)**

Chromatin remodeling proteins, Histone Modifiers and DNA Methyltransferases/demethylases



Gene	Tumours
Chromatin remodelling	
SMARCB1	Paediatric malignant rhabdoid tumours
SMARCA4	Lung adenocarcinoma, Burkitt lymphoma, medulloblastoma
PBRM1	Clear cell renal carcinoma
ARID1A	Ovarian clear cell carcinoma, hepatocellular carcinoma, colorectal cancer, lung adenocarcinoma
ARID1B, *ARID2*	Hepatocellular carcinoma, melanoma, pancreatic cancer, breast cancer
SMARCD1	Breast cancer
SMARCE1	Clear cell meningioma
ATRX	Paediatric glioblastoma, pancreatic neuroendocrine tumours
DAXX	Paediatric glioblastoma, pancreatic neuroendocrine tumours
CHD5	Neuroblastoma, glioma, breast, lung, colon, ovary, prostate cancers
CHD2	Chronic lymphocytic leukaemia
CHD1, *CHD3*, *CHD4*, *CHD6*, *CHD7*, *CHD8*	Gastric, colorectal, prostate, breast, bladder, serous endometrial cancers

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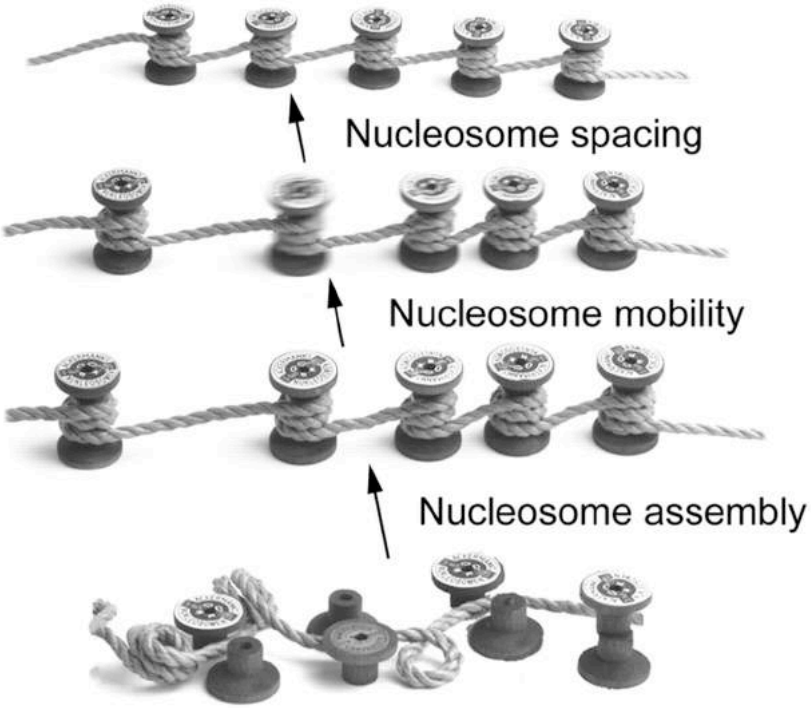
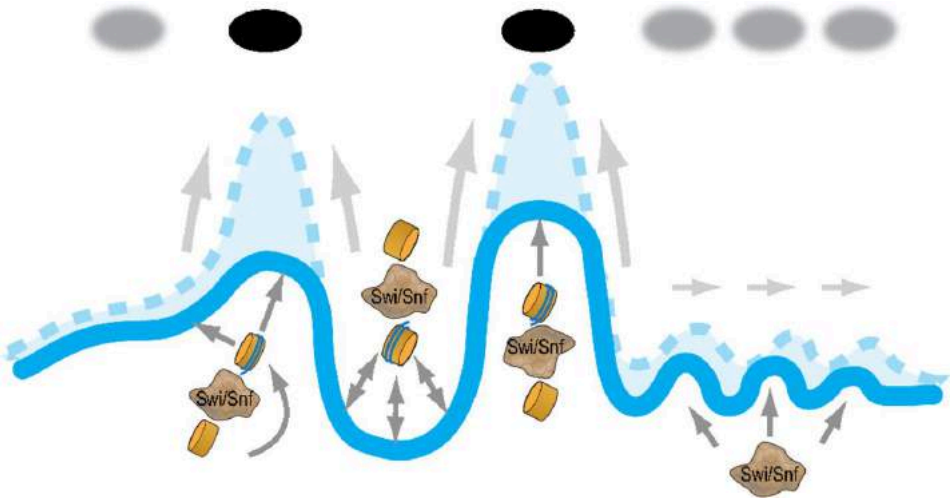
Chromatin Remodeling Complexes

ATP-dependent chromatin remodeling is one of several mechanisms that permit the compaction and decompaction of DNA in the nucleus while retaining the capacity for replication, selective gene expression, and DNA repair and recombination.



Swi/Snf sculpts the promoter-associated nucleosome landscape of a gene.



These complexes derive energy from the alternative ATPases Brg or Brm, which are paired with a second ATPase, β-actin

Nucleosomes thought to be the primary target of the complexes: *in vitro* transcription on nucleosomal templates -> complexes can phase or position nucleosomes, exchange nucleosomes, induce nucleosome mobility, evict nucleosomes, or relax torsional stress possibly by direct actions on nucleosomes

E.

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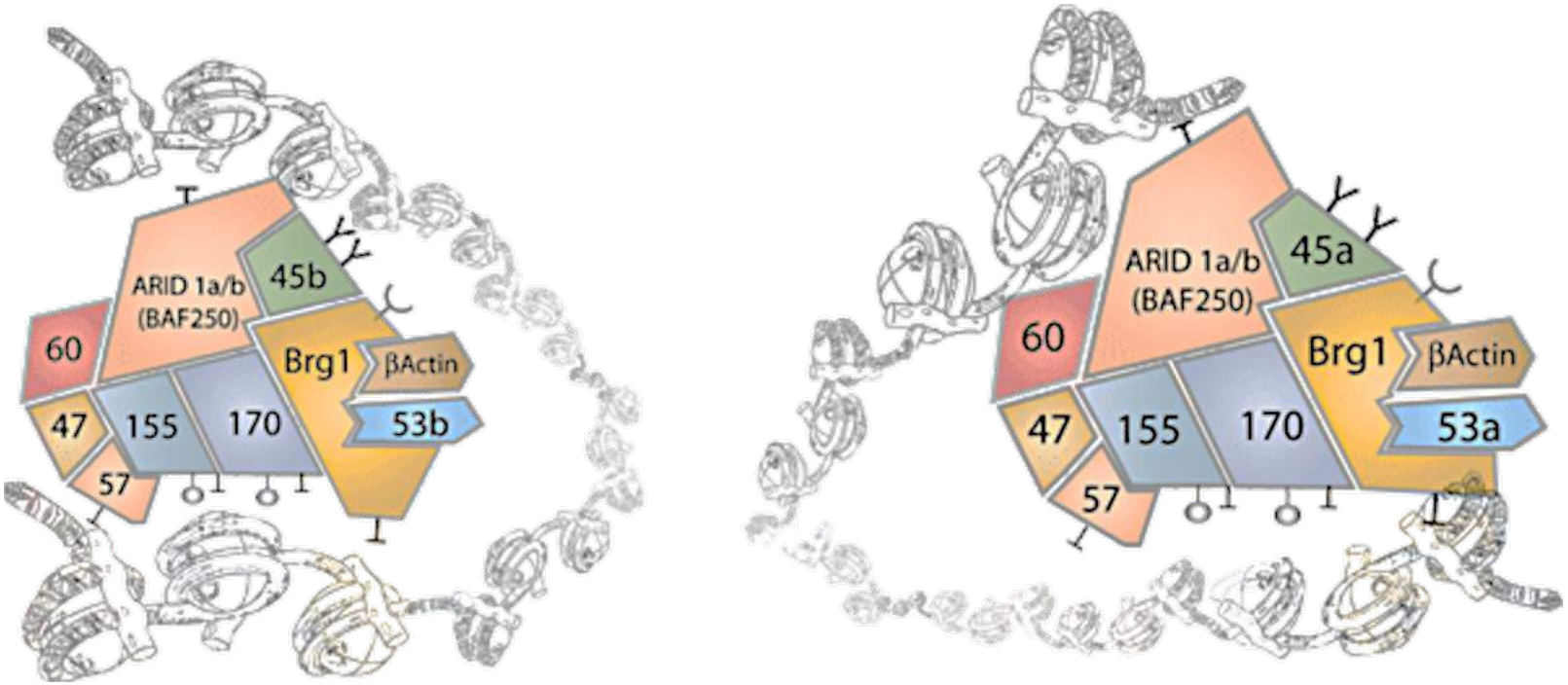

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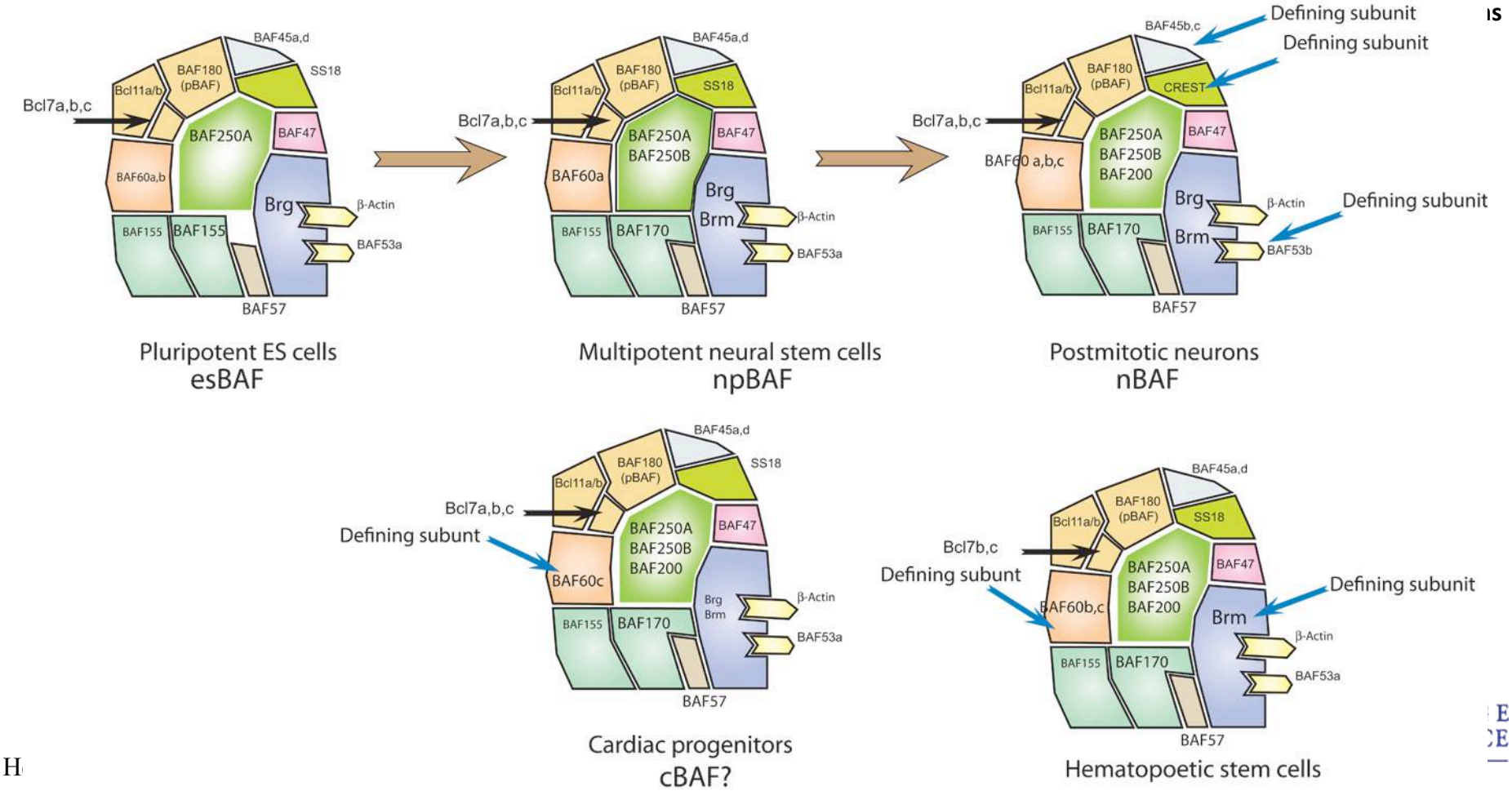
At least 29 genes encoded by 15 gene families
Some subunits are highly tissue-specific

Eg **BAF53b (an actin-like molecule), BAF45b** [a (PHD) finger protein], and CREST (*SS18L1*) (a Ca^{2+}-responsive

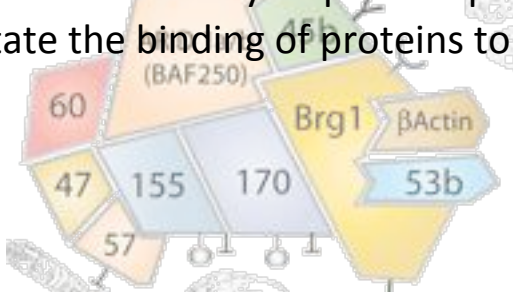


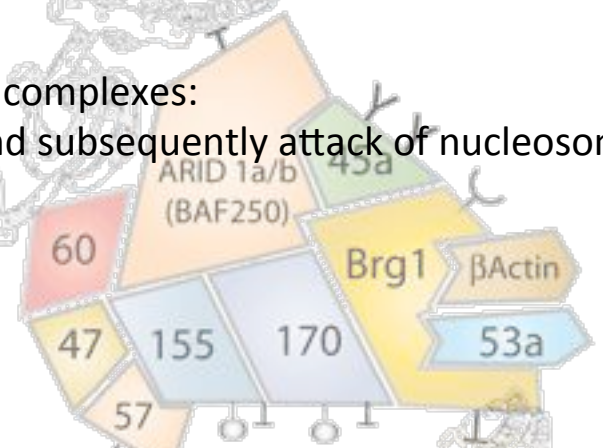
Chromatin Remodeling Complexes

ATP-dependent chromatin remodeling is one of several mechanisms that permit the compaction and decompaction of DNA in the nucleus while retaining the capacity for replication, selective gene expression, and DNA repair and recombination.

Mammalian SWI/SNF or BAF complexes may act to counteract Polycomb complexes (eg mutation of the ATPase Brg1 (*Smarca4*) of BAF complexes leads to H3K27Me3 accumulation and repression of many genes in embryonic stem (ES) cells – Crabrtree lab

Initial models for action of ATP-dependent chromatin remodeling complexes:
Recruitment to DNA by sequence-specific transcription factors, and subsequently attack of nucleosomes to facilitate the binding of proteins to DNA.





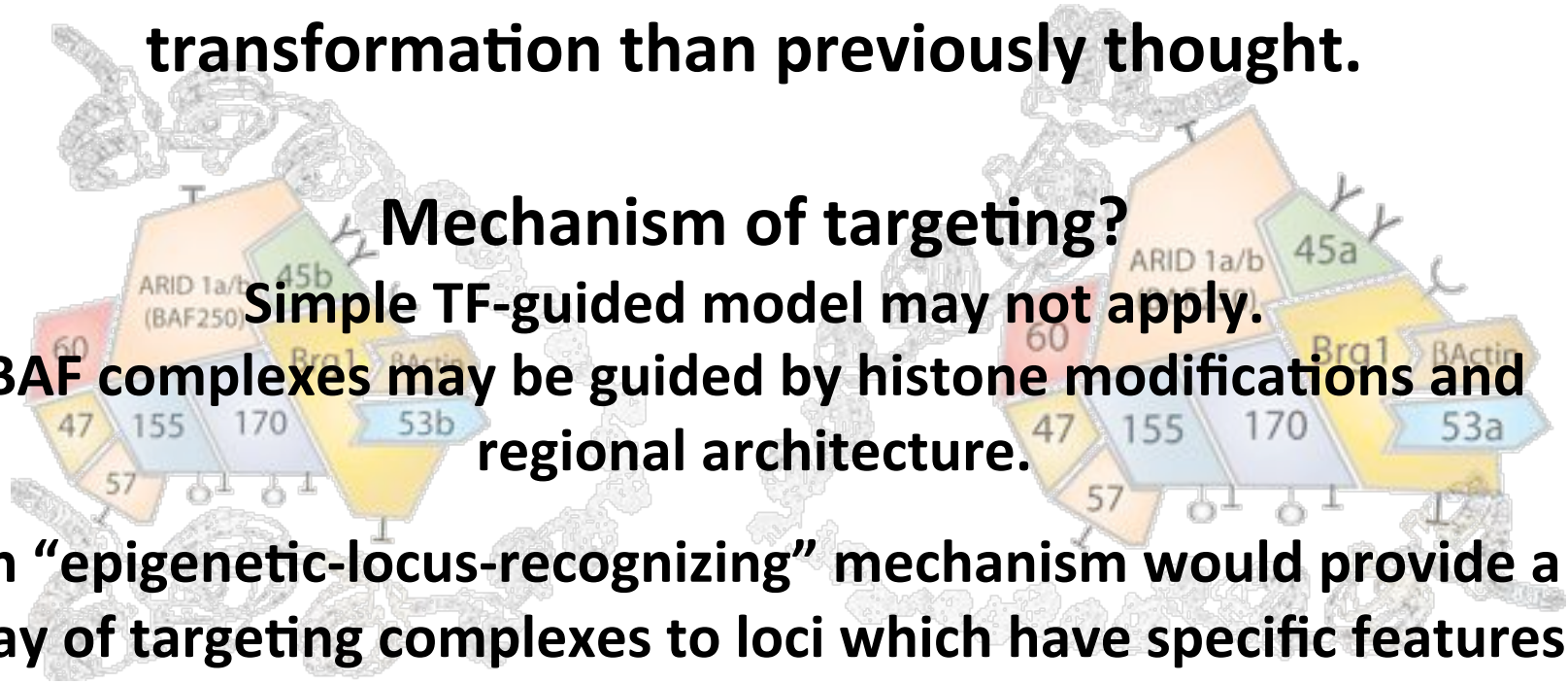
However, discovery that the deletion of subunits that gave the **strongest phenotypes** in mice were **not** required for *in vitro* chromatin remodeling opened up the question of **how** these subunits (and complexes) were functioning?

Instructive functions of these complexes were discovered in the conversion of fibroblasts to induced pluripotent stem cells and the conversion of human fibroblasts to neurons – and in cell type specification.

Genomic studies conducted on a number of human diseases have shown that **the subunits most commonly mutated** in human disease (cancer, neurodeveloppmental) were **not** those required for *in vitro* chromatin remodeling (nor for TF-directed targeting…)

Chromatin Remodeling Complexes

Chromatin remodeling complexes have a far more important and instructive role in reprogramming and transformation than previously thought.



Mechanism of targeting?

Simple TF-guided model may not apply.

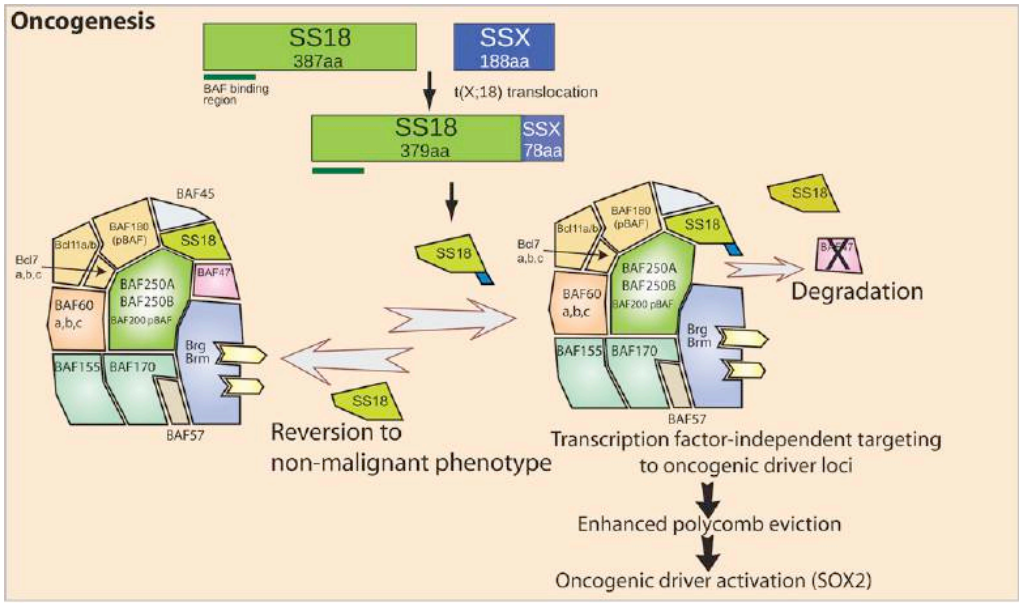
BAF complexes may be guided by histone modifications and regional architecture.

An "epigenetic-locus-recognizing" mechanism would provide a way of targeting complexes to loci which have specific features due to previous developmental events

Thus enabling access to specific groups of genes with particular chromatin signature

Chromatin Remodeling Complexes in Cancer

- More than 20% of human cancers bear a mutation to one subunit of 15-subunit of mSWI/SNF (BAF) complex
- Mutations can be heterozygous or homozygous, somatic or germline, result in deletion point mutation, or translocation resulting in protein fusions.
- BAF Complexes can be oncogenes as well as Tumor Suppressors
- Synovial sarcoma (nearly untreatable cancer of young people) – is always due to a t(X;18) translocation, fusion of part of SSX protein to SS18 BAF subunit



Fusion protein enters the BAF complex, displacing wild-type subunit as well as BAF47 (hSNF5), which is then degraded. The aberrant complex then binds the silent *Sox2* locus, which drives proliferation. The BAF complex probably activates Sox2 by removal of polycomb-placed H3K27Me3-repressive marks
(Kadoch and Crabtree, Cell, 2013)

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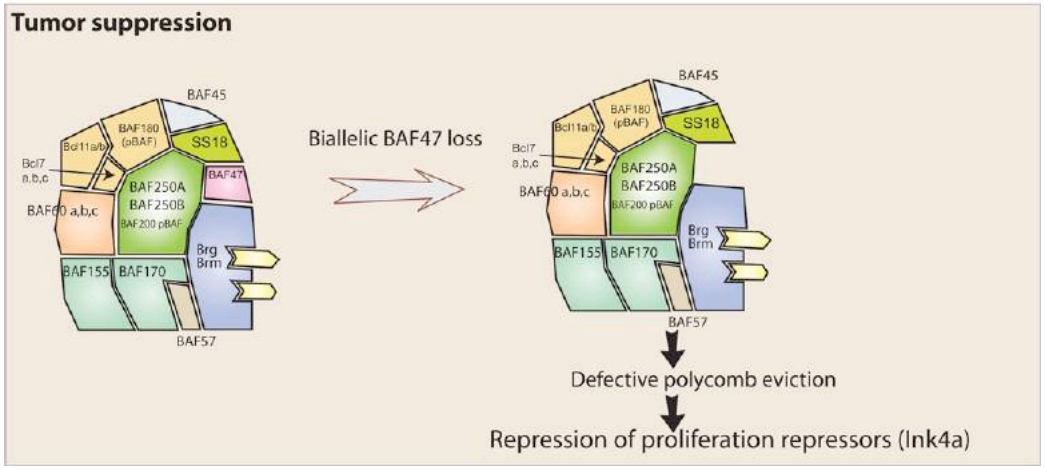
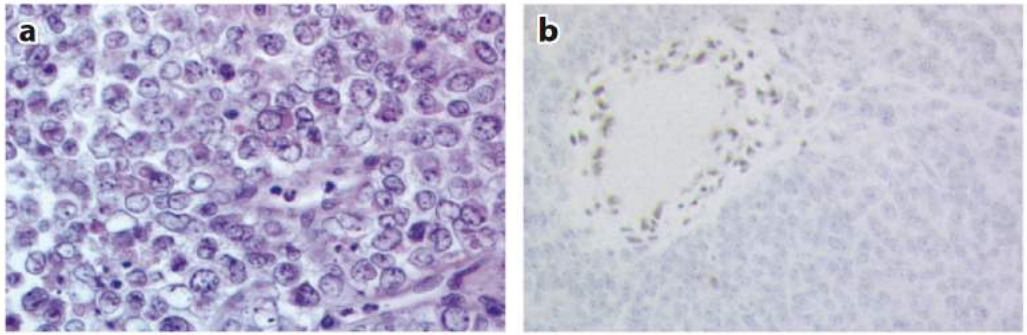
• BAF47 (SMARCB1, INI1, hSNF5) is always lost in **malignant rhabdoid tumors (MTRs)**

- Primarily kidney tumor, in children (~<2yrs)
- MRTs have the lowest mutation burden of all human tumors (except BAF47 mutation)

=> In fact – MTRs can be considered almost purely "epigenetic" tumors!



BAF47 mutant cells appear to be unable to remove PRC2 and H3K27me3 including from the Ink4a (Cdkn21) locus which normally suppresses proliferation
Cells are then transformed <u>without</u> additional mutations.



Rhabdoid tumor of the kidney: cells with prominent nucleolus in uncondensed chromatin and typical cytoplasmic eosinophilic inclusions.

Loss of BAF47 staining in the tumor cells

Versteege et al (1998) Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature 394:203-206.

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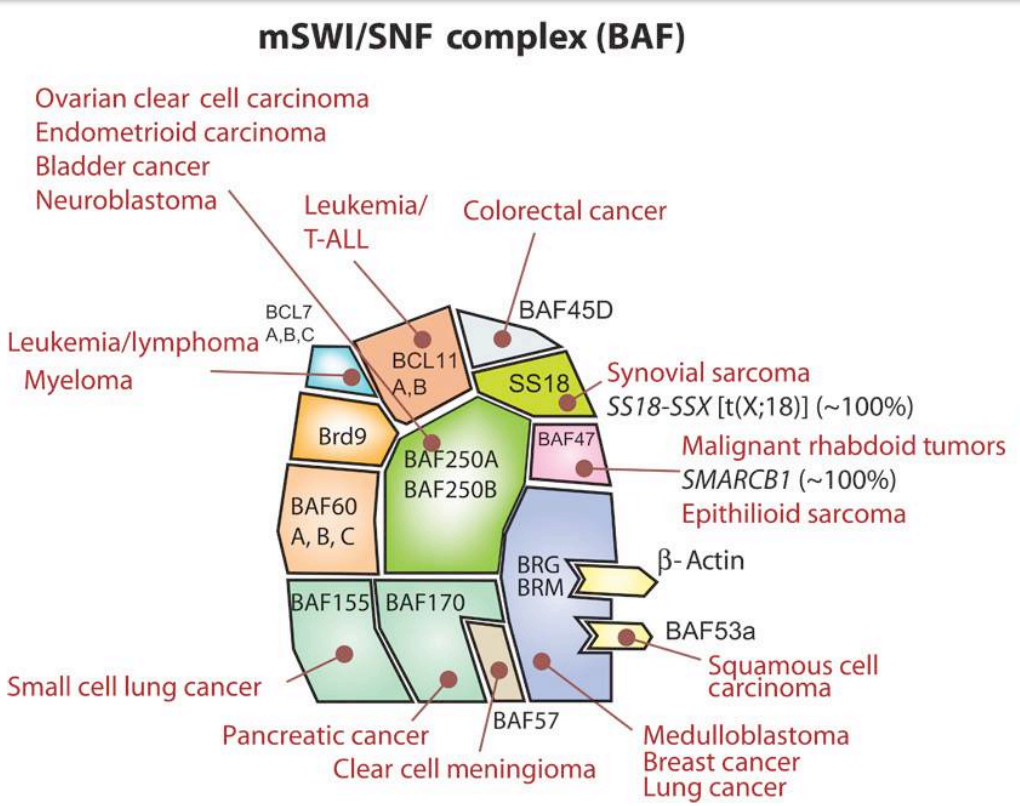
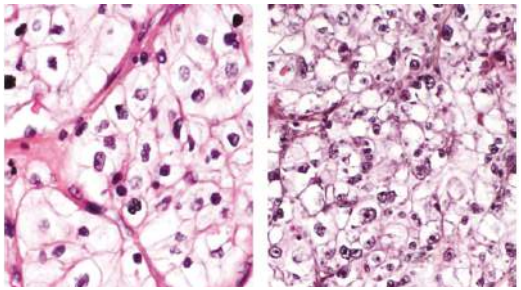
• **Other BAF subunits?**
- Often heterozygous mutation (dosage sensitive)
- Mainly adult cancers
- Very different tissues – specific subunits
- Various histological types - though a significant number of tumors exhibit a peculiar *clear cell morphology* – may be linked to excessive glycogen accumulation as a consequence of abnormal carbohydrate metabolism?



• BAF250A (ARID1A) – most common BAF subunit mutation in cancer - ovarian clear cell carcinomas (dedicated to the complex; but NOT involved in *in vitro* chromatin remodeling).

• BAF57 (SMARCE1) – only mutated in non-NF2 multiple spinal meningiomas.

• BRG ATPase - mutated in >90% small cell ovarian cancers, but <5% small cell lung cancers.



Excessive cytoplasmic accumulation of substances such as glycogen, lipid droplets, mucosubstances, or mucin vacuoles

E. Heard, 2016

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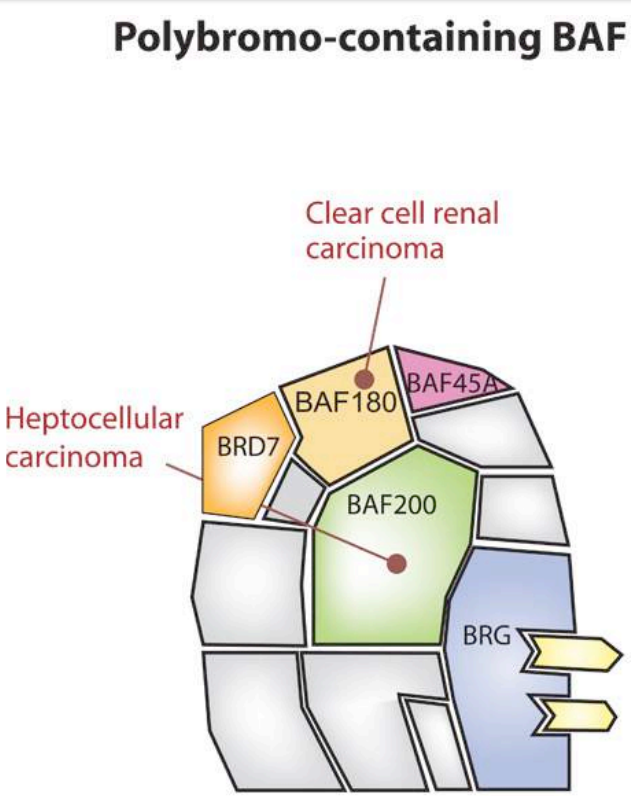

• **pBAF complex in cancer:**
- pBAF contains polybromo (PBRM1 or BAF180); BAF200 (Arid2); Brg (but not Brm) & otherBAF subunits
- BAF180 protein contains six bromodomains that are similar to the single bromodomain found in Brg1.
- BAF180 is mutated or deleted in more than 50% of clear cell renal cell carcinoma (ccRCC)

Mutation of <u>any single bromodomain</u> in one BAF180 allele is sufficient to contribute to cancer formation

NB at least 2 other genes near BAF180, VHL (ubiquitin ligase); BAP1 (deubiquitinase) fromsame region (3p) contribute to ccRCC independently…

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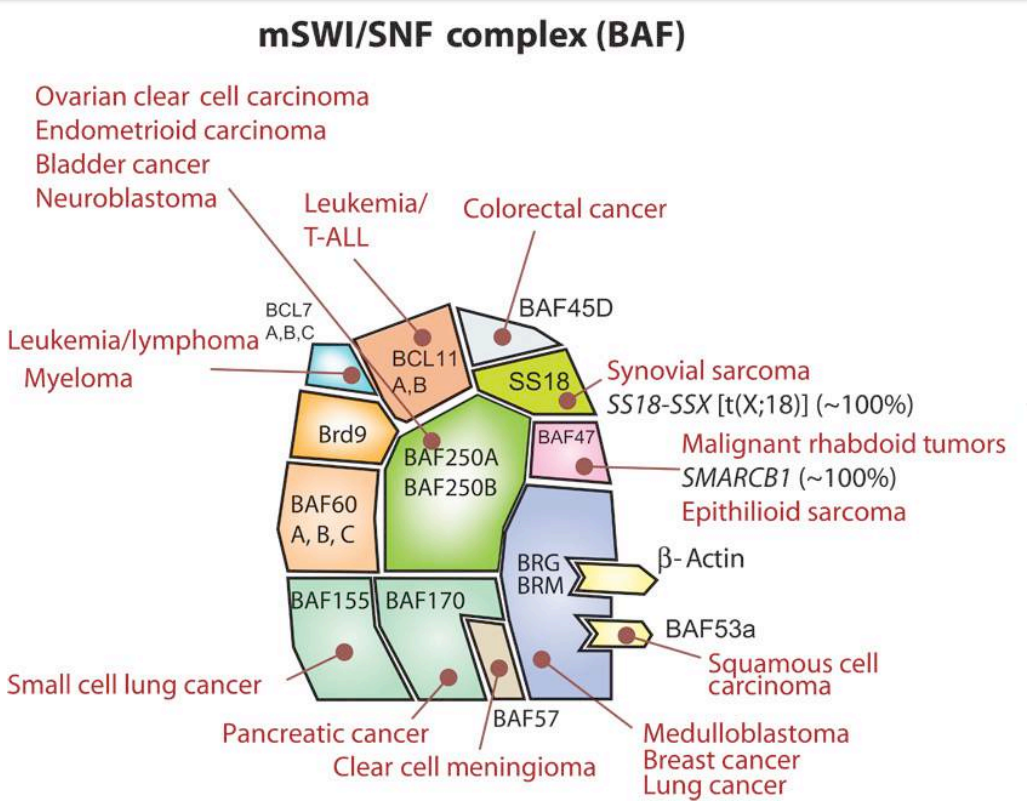

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Why such tissue-specificity: *Cell of origin*?

Why such dosage-sensitivity: *Complex stoicheometry*?

How do mutated subunits affect cancer?

E. Heard, 2016

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Chromatin Remodeling Complexes in Cancer

BAF-Polycomb antagonism

Human BAF47 mutation: Rhabdoid Tumors by 2yr of age

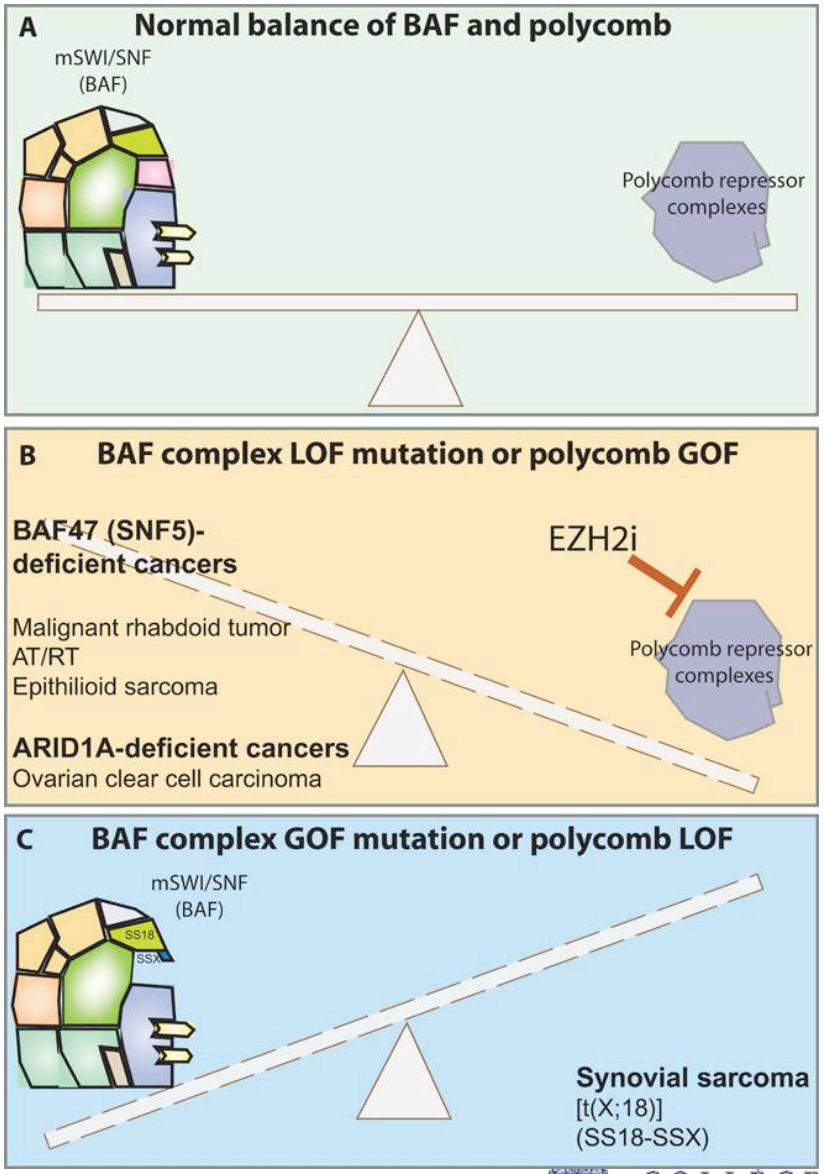
Mouse conditional knock out -> T cell lymphomas: very short latency (Wilson et al, Cancer Cell, 2010)

⇒ Although mouse model give different tumor type pathogenesis may be similar:

BAF complexes in the mutant cells are unable to remove Polycomb complexes and H3K27Me3, from the Ink4a (*Cdkn2a*) locus, which normally suppresses proliferation

Nearly all of the effects of BAF47 loss could be explained by accumulation of polycomb and its products over the Ink4a locus indicated that polycomb inhibitors may be effective in these cancers.

However mechanism by which loss of BAF47 leads to a failure to remove Polycomb is still unclear…



Chromatin Remodeling Complexes in Cancer

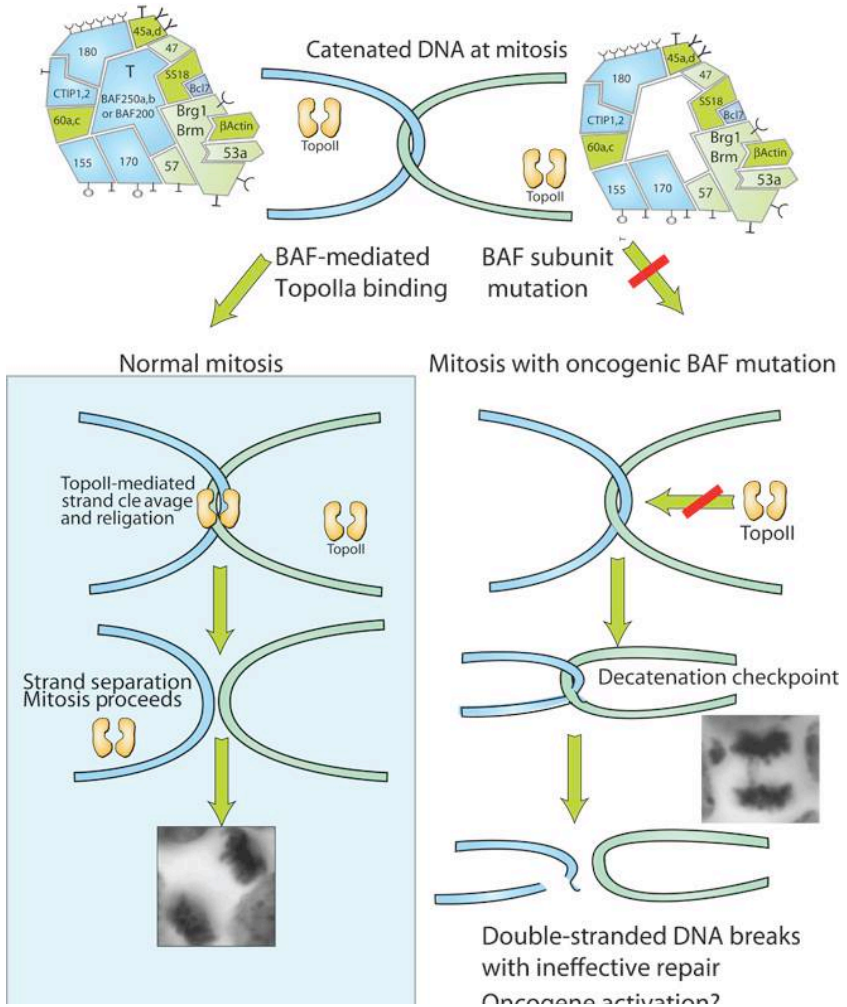
BAF-Topoisomerase II synergy

BAF co-purifies with Topo11a and is necessary for binding of TopoIIa to DNA at 70% of its genomic sites

Rapid conditional deletion of oncogenic BAF subunits leads to cell cycle arrest with anaphase bridges, due to inability of cells to untangle DNA at anaphase, normally the job of TopoII.

The mechanism by which DNA is repaired after possibly being cleaved in the cytoplasm by cytoplasmic DNase is unclear, but may be error-prone and lead to an accumulation of mutations.

BAF helps TopoII resolve tangled DNA, allowing it to segregate normally to daughter cells. When an oncogenic subunit of the BAF complex is mutated, DNA is not untangled at anaphase, leading to breaks with defective repair.



As BAF subunit mutations prevent TopoII from contacting DNA, prediction is that cancers with BAF subunit mutations should be resistant to TopoII inhibitors. This may be helpful in guiding the use of these highly toxic inhibitors.

Mutations in Epigenetic Regulators: The Backseat Drivers of Cancer?

Many driver mutations in oncogenes and tumors suppressors now identified

Driver or Passenger Mutations

De Carvalho *et al Cancer Cell 2012*
& Nature Rev. Cancer 2012

Mutations in <u>epigenetic regulators</u> can have a widespread impact on gene expression, genome stability thereby producing multiple potential new phenotypes within a single tumor

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Année 2015-2016 :
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6 avril, 2016

Cours VI

"Perspectives: Marqueurs et thérapies épigénétiques ”
“Epigenetic Biomarkers and Therapies”

Seminar by Prof. Kristian HELIN
(Director of the BRIC, Copenhagen, Denmark)
“Epigenetic Targets in Cancer”

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