Cancer and Epigenetics

From Stem to Cancer

Brian Wiley

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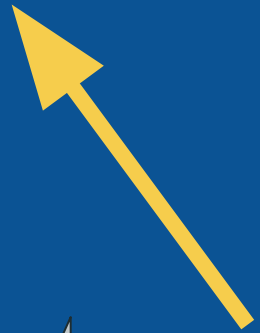
Chris Sohn



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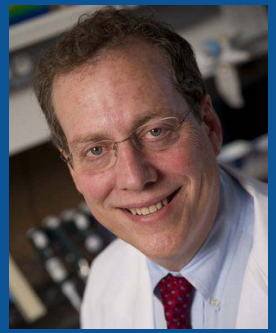
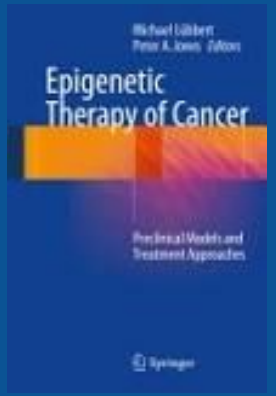
Inspiration





Researchers at Johns Hopkins : SB Baylin, AP Feinberg

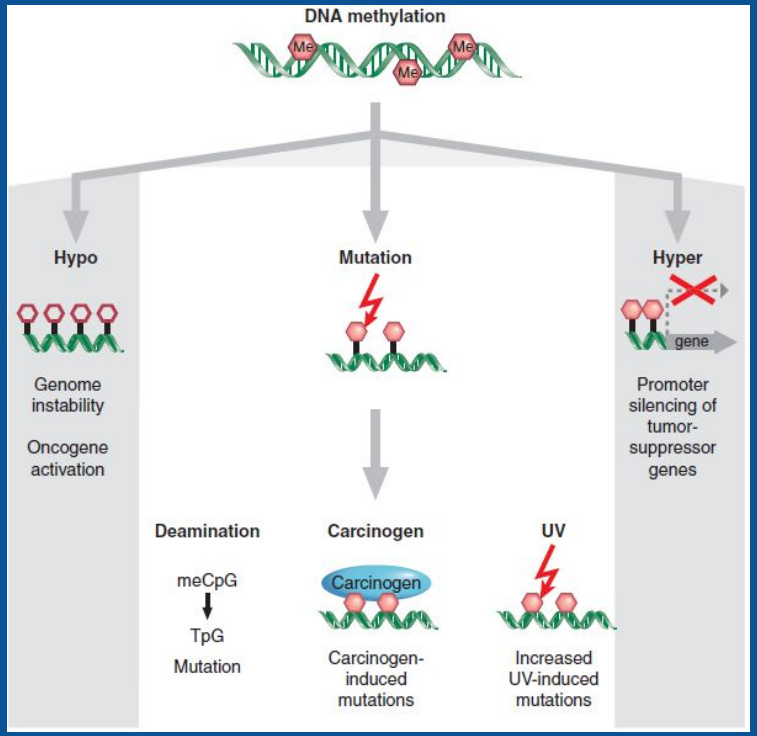
Van Andel Research Institute: PA Jones

"Cancer Stem Cells (CSCs) have shown to be more resistant to anti-tumor treatments than the non-stem cancer cells, suggesting that surviving CSCs could be responsible for tumor relapse after therapy." (Munoz et al 2012) [12]

"CSCs are the likely source of resistant cells responsible for disease relapse because cells deprived of self-renewing potential are unable to reconstitute the cancer even if they survive treatment." (Wainwright & Scaffidi 2017) [13]

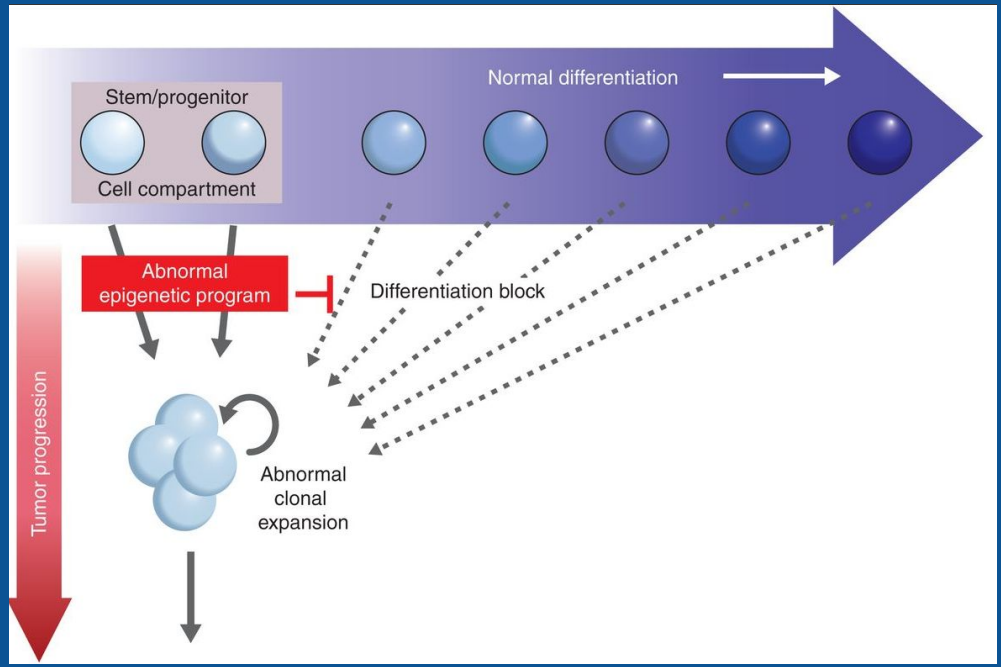
Role of DNA Methylation in Cancer

- **As described by Baylin and Jones in Ch. 34, the three epigenetic modifications proposed in the diagram will in tandem contribute to cancer.**
  - **general hypomethylation of the cancer genome leading to genome instability and aneuploidy**
  - **hypermethylation of CpG islands in 5' regions of tumor suppressor genes**
  - **mutagenesis of the methylated cytosines through UV exposure or other environmental factors**



Chapter 34 Intro

- **Figure from Ch. 34 describing abnormal programming early in differentiation of a progenitor.**
  - **If the abnormality isn't taken under control here, it will lead to tumor progression.**
- **Abnormal clonal expansion**
  - **At risk of epigenetic changes**



What is the Epigenetic Progenitor Model of Cancer?

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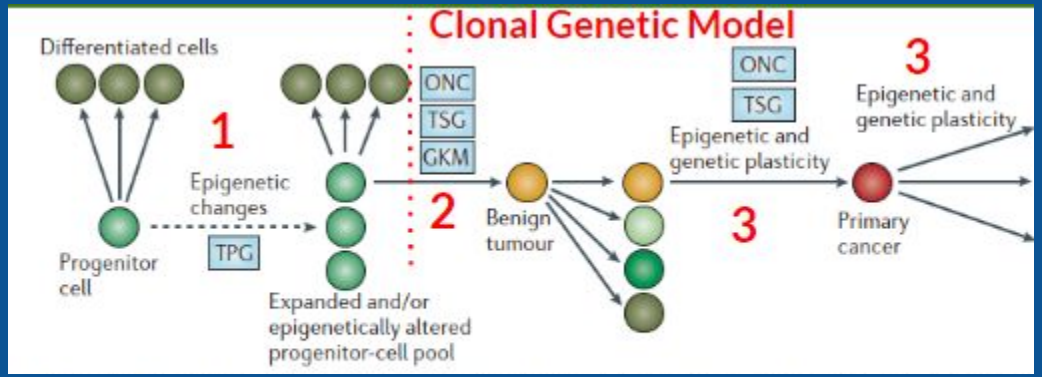
1. **Challenges the original view on cancer**
   a. **Instead dependent on epigenetic changes**



1st Step — epigenetic disruption of progenitor cells

1. **The first step — epigenetic disruption of progenitor cells**
2. **The second step — initiating mutation.**
3. **The third step — genetic and epigenetic plasticity.**

1st Step — epigenetic disruption of progenitor cells

Leads to polyclonal precursor population of progenitor stem cells that are “neoplastic ready”

Disruption of balance between undifferentiated progenitors and lineage committed cells.

Class what could be some reasons?

What could be some reasons?

1. **DNA methyltransferases and TPGs**
2. **Balance of Homeobox (HOX) protein expression regulated by PcG and TrxG.**
3. **PcG and TrxG protein themselves. E(Z)/EZH1/2 HKMT (SET domain) for H3K27me3.**
4. **Imprinting?**
5. **Many other genes such as ...**

Is there Evidence?

Five lines of evidence

Five lines of evidence suggesting evidence of an epigenetically disrupted progenitor cells (Feinberg et al., 2006)

1. **Reversible tumor growth properties**
2. **All tumors show global methylation changes and even normal (non-tumour) tissue show same or similar methylation status.**
3. **Melanoma nucleus can give rise to a normal mouse showing reprogramming potential**
4. **Neoplastic cells can only be maintained by cells with stem cell properties**
5. **Loss of imprinting can lead increase in progenitor cell population**

YS

Five lines of evidence 1

Five lines of evidence suggesting evidence of an epigenetically disrupted progenitor cells (Feinberg et al., 2006)

1. **Reversible tumor growth properties**
   - study was done in leukemic cells.

Explained in detail in Brian's motivational part

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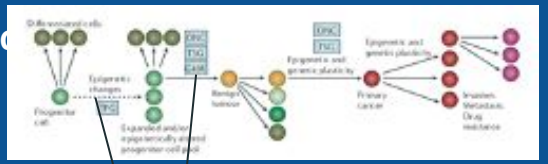
Five lines of evidence 2

Five lines of evidence suggesting evidence of an epigenetically disrupte progenitor cells (Feinberg et al., 2006)



Same time?

The epigenetic progenitor model of cancer

2. <u>All</u> tumors show global methylation changes and even normal (non-tumour) tissue show same or similar methylation status.

- how can global methylation change and single mutation change occur at the same time?
- there is epigenetic footprint in tumor and non tumors , how do you explain cells with no mutations?

DNA methylation changes comes before genetic changes

Five lines of evidence 3

Five lines of evidence suggesting evidence of an epigenetically disrupted progenitor cells

3. Melanoma nucleus can give rise to a normal mouse showing reprogramming potentials

- two step procedure
  i. somatic Nuclear Cell Transfer (SCNT) of melanoma nucleus into enucleated oocyte
  ii. extracted ESCs from blastocyst and plated to grow ESC lines that were tumorigenic
  iii. injected tumorigenic ESCs into new tetraploid blastocysts

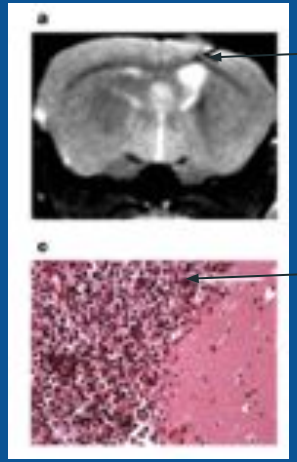
- **almost all the tumor properties were reversed (although some mice had increased incidences of tumors)**

YS

Five lines of evidence 4

5 lines of evidence suggesting evidence of an epigenetically disrupted progenitor cells

4. **Neoplastic cells can only be maintained by cells with stem cell properties**
   - **of the brain tumor cells grafted into NOD-SCID mice, only $CD113^{+}$ can initiate tumours in mice while $CD113^{-}$ brain tumor cells could not**



Injection of CD133+ tumor cells shown by arrowhead

a. MRI scan of mouse
b. Magnification of histogram

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Five lines of evidence 5

5 lines of evidence suggesting evidence of an epigenetically disrupted progenitor cells

Explained in detail in Chris's portion

5. Loss of imprinting

- **biallelic expression of Igf2 (Instead of paternal IGF2 and maternal H19nc) lead to shift in balance toward increased ratio progenitor to differentiated cells.**

2nd Step - initiating mutation

1. The first step — epigenetic disruption of progenitor cells
2. **The second step — initiating mutation.**
3. The third step — genetic and epigenetic plasticity.

2nd Step - initiating mutation

Specific for tumour type:

B-cell and T-cell

Adenomatous polyposis coli (APC) mutation for Colorectal cancer

BCR-ABL for Chronic Myeloid Leukemia

Class can epigenetic alterations can drive tumorigenesis even without a single genetic mutation???

2nd Step - initiating mutation

“Epigenetic alteration can substitute for mutation-induced oncogene activation or tumour-suppressor gene silencing”

(Feinberg et al. 2006)

3rd Step - genetic and epigenetic plasticity

1. The first step — epigenetic disruption of progenitor cells
2. The second step — initiating mutation.
3. **The third step — genetic and epigenetic plasticity.**

3rd Step - genetic and epigenetic plasticity

- **Ability for tumour to stably evolve - tumour microenvironment**
- **Genetic plasticity**
- **Epigenetic changes**
  - Centromere protein H (CENPH) upregulated in cancer
    - Results in aneuploidy
  - DNMT1, ↑ PRC2's EZH2, other Histone marks

PART 2

Chris - Colorectal and Epigenetics

Brian - Hematological Cancers

Yea Ji - Ageing and Cancer

WITH BONUSES IN BIOINFORMATICS!

Part 2 - Colorectal Cancer, Loss of imprinting[1]

- Previously in the Clonal genetic model
  - Shortcomings include inability to explain specific stages of tumor development
- Loss of imprinting (LOI)
  - LOI of the insulin growth factor 2 (IGF2)
    - This LOI causes an increase in progenitor cells in the kidney in Wilms tumors in children and in the GI tract in patients with colorectal cancer.

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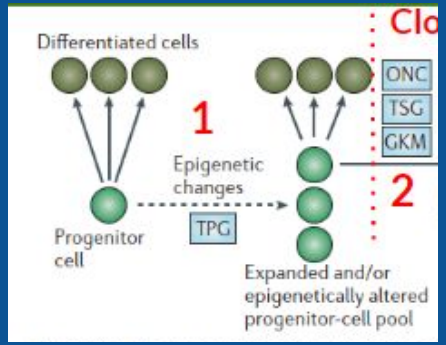
Colorectal Cancer, Loss of imprinting[1]

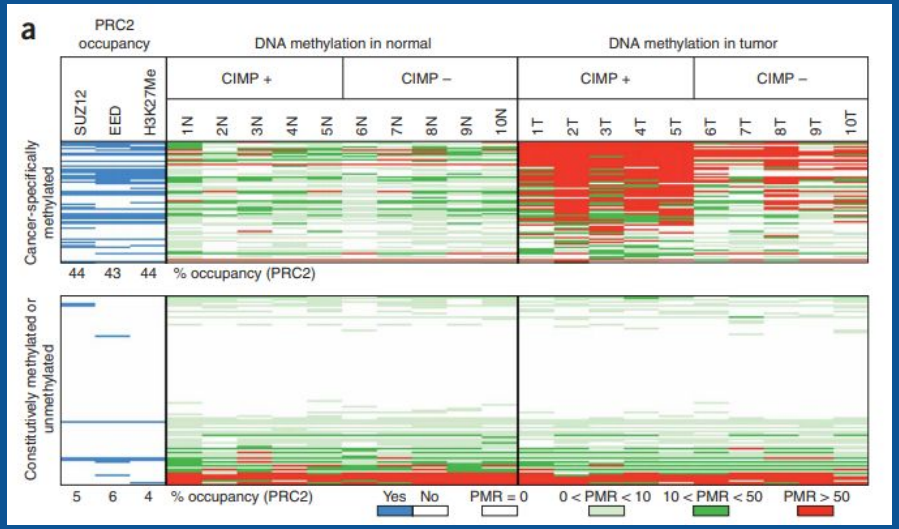


- **IGF2 - a tumor progenitor gene**
  - LOI leads to increase in progenitor cell compartment
- **Thinking back to the Epigenetic Progenitor Model**

- Loss of imprinting of *IGF2* (insulin-like growth factor 2) is common in the normal colonic epithelium of patients that are at risk of colorectal cancer, and mouse studies show that this epigenetic change shifts the balance of the intestinal epithelium towards an expanded progenitor-cell population[46,47,65]. Altered methylation is also found in the stroma of cancer patients[88,146].

Bioinformatics Application Colorectal Cancer[3]

- **ChIP-seq was used to obtain PRC2 data**
  - Polycomb repressive complex 2 (PRC2) upregulation
- **DNA Methylation using a MethyLight assay[14].**



Part 2 - Hematological Cancers

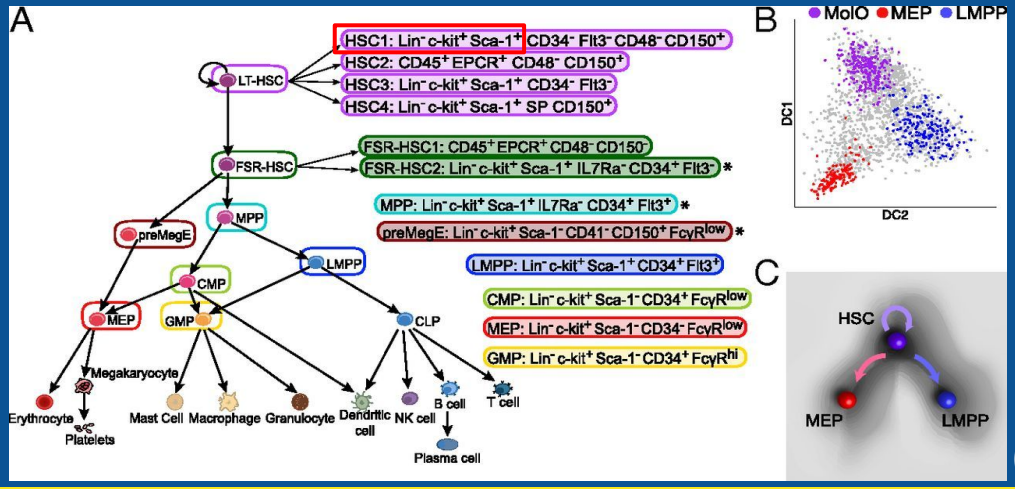
DNA Methylation role in blood cell development

- **DNMT1**
- **DNMT3A**
- **TET2**

HoxA9 and Meis1 role in HSC self-renewal

Hematopoietic stem cells (HSCs)

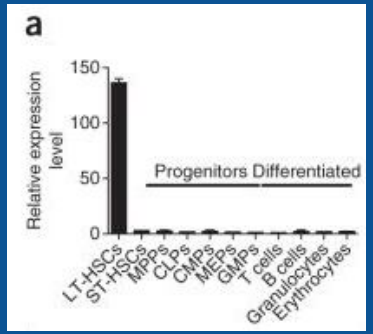
- **Hematopoietic stem cells reside in the bone marrow**
- **Defined by their capacity for the lifelong maintenance of blood and bone marrow**
- **Achieved through their differentiation into a myriad of cell types, as well as the regeneration of stem cells via self-renewal. (Challen et al. 2011)** [4]

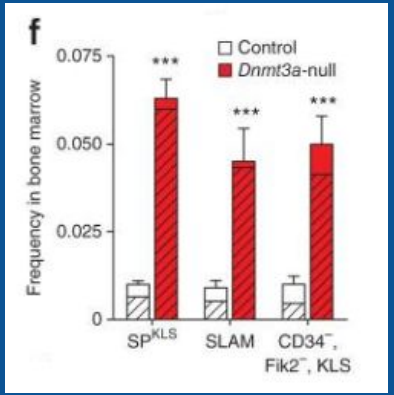


(Hamey et al. 2016) [5]

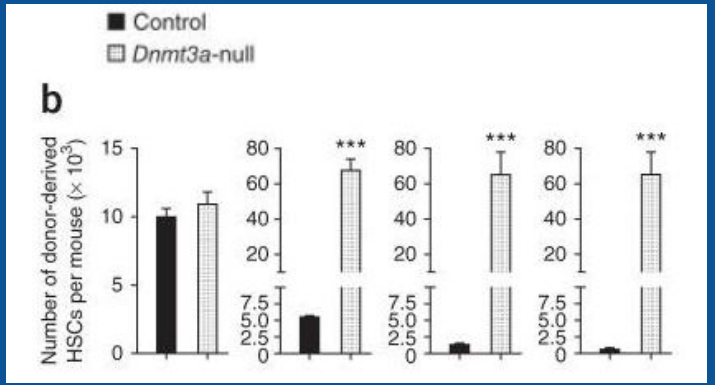
HSCs and Hematopoiesis

Dnmt3a critical in the epigenetic silencing of HSC regulatory (self-renewal) genes, thereby enabling efficient differentiation. (Challen et al. 2011) [4]





Dnmt3a-null HSCs again regenerated remarkable numbers of HSCs, with an average of 50-fold more HSCs derived from Dnmt3a-null cells than from their control counterparts. (Challen et al. 2011) [4]



Relation to Hematological Malignancies

741 hypomethylated DMRs associated with 434 genes in Dnmt3a-null HSCs. Many of the hypomethylated genes are commonly associated with human hematopoietic malignancies, such as Prdm16, Stat1, Ccnd1, Myc, Mn1, Msi2, Men1, Erg and Runx1. (Challen et al. 2011) [4]

chrom	chromstart	chromend	cpgSites	Dnmt3a-KO methRatio	Dnmt3a-KO allCpgCount	Control methRatio	Control allCpgCount	methDiff Dnmt3a-KO - Control	class Dnmt3a-KO vs Control	name2
chr7	152118448	152118503	4	0.04	628	0.68	635	-0.63	strongHypometh	Ccnd1
chr16	95822656	95822887	7	0.28	558	0.77	361	-0.49	strongHypometh	Erg
chr19	6339713	6339847	4	0.37	218	0.86	120	-0.49	strongHypometh	Men1
chr5	111848806	111849222	23	0.20	3263	0.57	2258	-0.37	strongHypometh	Mn1
chr5	111848245	111848373	3	0.07	155	0.57	221	-0.50	strongHypometh	Mn1
chr5	111935613	111935639	4	0.28	791	0.77	97	-0.49	strongHypometh	Mn1
chr11	88374826	88374874	3	0.44	377	0.93	303	-0.49	strongHypometh	Msi2
chr15	61813178	61813269	4	0.31	296	0.82	156	-0.51	strongHypometh	Myc
chr4	154001112	154001225	5	0.14	842	0.73	263	-0.59	strongHypometh	Prdm16
chr4	153895314	153895422	3	0.14	194	0.81	81	-0.68	strongHypometh	Prdm16
chr16	92695896	92696188	18	0.34	3027	0.83	1210	-0.49	strongHypometh	Runx1
chr1	52174091	52174134	4	0.14	1952	0.78	235	-0.64	strongHypometh	Stat1
			?		?		?			

Relation to Hematological Malignancies

434 Dmnt3a-KO hypo-methylated genes

Oncomine Concepts	Overlapped Genes	adjusted p-value
Cancer Gene Census - all causal cancer genes	18	2.76E-05
Acute Myeloid Leukemia - CBFB-MYH11 Gene Fusion - Top 10% Over-expressed (Valk Leukemia)	58	5.25E-04
Acute Lymphoblastic Leukemia - BCR-ABL1 Gene Fusion - Top 1% Over-expressed (Ross Leukemia)	14	6.00E-03
B-Cell Acute Lymphoblastic Leukemia - Top 5% Over-expressed (Haferlach Leukemia)	51	2.67E-06
KEGG Pathways		
mmu05200:Pathways in cancer	21	1.50E-02

Aff3, Arhgef12, Bcl3, Brca2, CCND1, Col1a1, Epas1, Erg, Etv6, Fnbp1, Hip1, Mecom, Men1, Mn1, Msi2, Myc, Notch, Pdgfrb, Prdm16, Ptch1, Rbm15, Runx1, Smad3

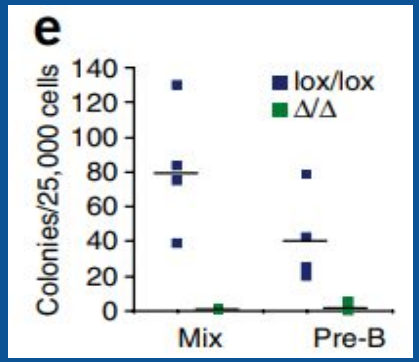
DNA Methyltransferases

Is there treatment to mutant Dnmt3a in certain types of leukemias?

Class what about other DNMTs? Do you hypothesize same or similar results?

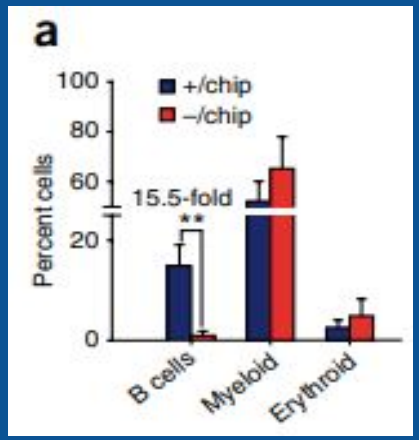
HSCs and Hematopoiesis - A Little Complicated?

Completed Dnmt1 knockout, mice HSCs were not able to differentiate to myeloid or B-cell.



Blue = Dnmt1+/+
Green = Dnmt1 -/-
Mix = Myeloid and B-cell

Notably, HSCs from mice with reduced [Dnmt1] activity cannot suppress key myeloerythroid regulators and thus can differentiate into myeloerythroid, but not lymphoid, progeny. (Bröske et al) [6]



Blue = Dnmt1+ / Dnmt1 hypomorphic

Orange = Dnmt1- / Dnmt1 hypomorphic

Ablation DNMTs -> Leukemia or Lymphoma more likely?

HSCs and Hematopoiesis - Even more Complicated??

Research Focus. **MLL-AF9** is the most frequent **MLL** rearrangement in childhood acute myeloid leukemia (AML) and it may be also found in acute lymphoblastic leukemia (**ALL**) of patients younger than 1-year-old (infants).

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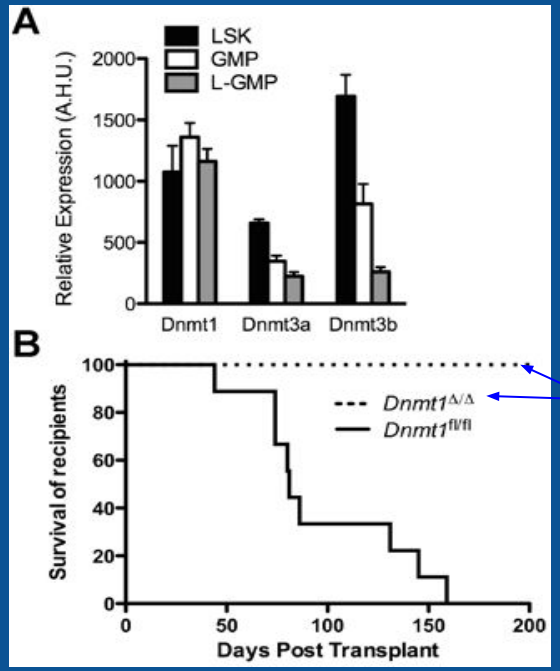
MLL-AF9 - Thermo Fisher Scientific

Department of Pediatric Oncology,
Dana-Farber Cancer Institute



(Trowbridge et al. 2012) [10]

LSK: Lin Sca-1+ c-Kit+ (HSCs)

GMP: granulocyte–macrophage progenitors

L-GMP: leukemic granulocyte–macrophage progenitors

Excerpts from (You and Jones 2012) [7]

Recent studies uncovered a role of DNMT3A in silencing self-renewal genes in hematopoietic stem cells (HSCs) to permit efficient hematopoietic differentiation and its loss progressively impairs HSC differentiation (Challen et al., 2011; Trowbridge and Orkin, 2011).

All known DNMT3A mutations are related to poor survival in AML(Ley et al., 2010; Yan et al., 2011), suggesting that these mutations prevent differentiation and have an important role in the progression of disease. (You and Jones) [7]

Notably, TET2 loss-of-function mutations were mutually exclusive of mutations in IDH1 (isocitrate dehydrogenase1) and IDH2, which are known to induce DNA hypermethylation and impair differentiation in hematopoietic cells (Figueroa et al., 2010).

YJS

Polycomb group targets (Teschendorff et al., 2010) [19]

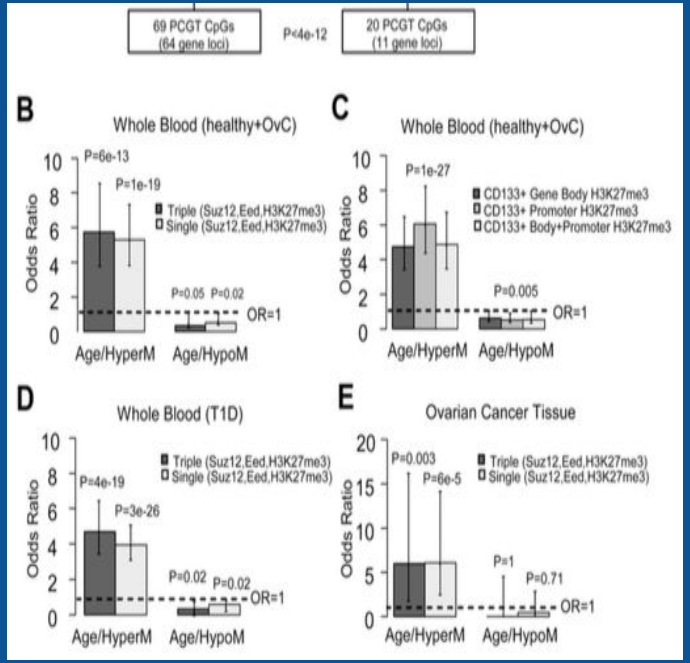
- Hypothesis using two connection
  1. promoters of PCGT that is methylated in cancer [19]
  2. cancer increases with age as with methylation changes
- Study definition of PCGT
  - Promoter occupancy at CpG of SUZ12, EED or H3K27me3 in hESC [19]
- Tested on blood cells and epithelial cells to see age-PCGT CpG methylation signature [19]
- See this level in cancer
- Study method (including stem cells in 1&2)
  1. age dependent signature from blood samples
  2. validation : in independent blood sample and epithelial tissue
  3. see these changes in cancerous epithelial tissue

Age related hypermethylation is independent of cell type

YJS

Independent of- “sex, disease, tissue, or cell type” [19]

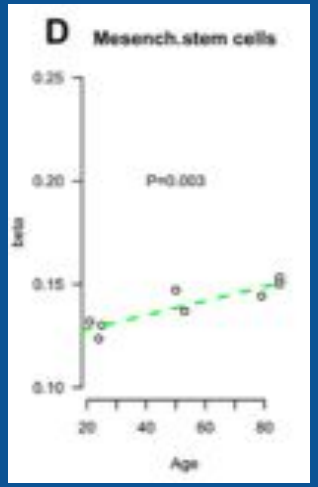
- **B. Fivefold increase in PCGT CpG, compared to non-PCGT CpG [19]**
- **C. Five Fold enrichment of H3K27me3 in PCGT CpG, specifically in HSC [19]**
- **D. T1D (female & male), enrichment of PCGT CpG [19]**
- **E. Ovarian cancer patients, enrichment of PCGT CpG [19]**



Y-axis: Enrichment odds ratio
X-axis: Donor age

Increased methylation seen in stem cells

Validation in MSC DNAm increase in 59/69 PCGT CpG [19]

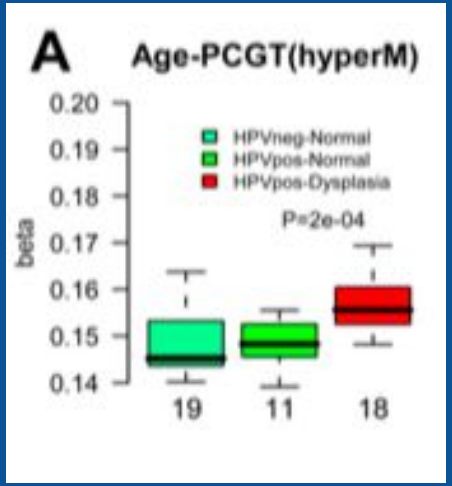


Y-axis: 69-age hypermethylated PCGT CpG
X-axis: Donor age

YJS

Increase in methylation due to age-can differentiate cancer vs. non-cancer

A. Increase in DNAm in cancerous tissue vs. normal tissue

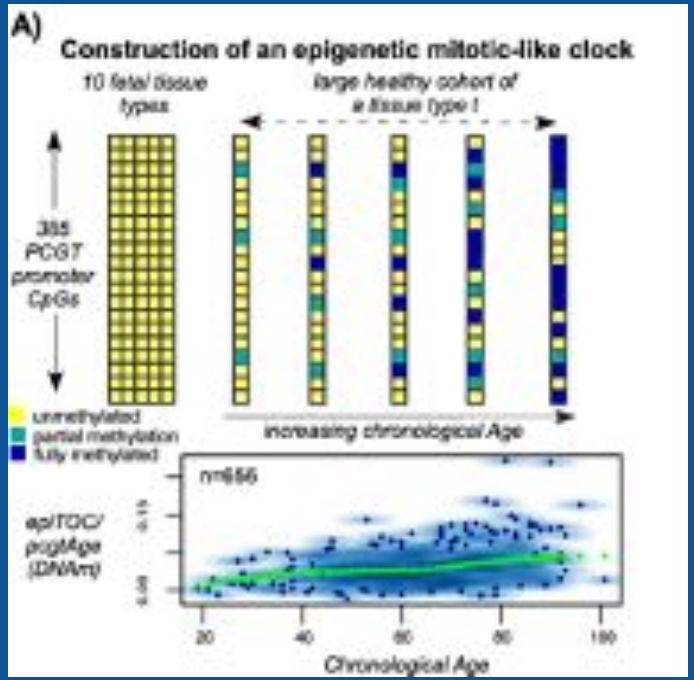


Y-axis: 69-age hypermethylated PCGT CpG
X-axis: from left to right
HPVnegative-Norm ((green)
HPVpositive-Normal (green)
HPVpositiv-Dysplasia (red)

Application of PCGT-Epigenetic Timer Of Cancer (epiTOC) (Yang et al., 2016) [21]

YJS

- **epiTOC**
  - It can predict cancer due to stem cell alterations (division rate) caused by increased methylation at PCGT CpG
- **Requirement for epiTOC**
- **CpG criterias**
  1. unmethylated CpG in fetal tissue types
  2. CpGs mapped for PCGT as stated previously
  3. CpGs methylation that is increased with age at PCGT



epiTOC shows increase in methylation with age-in all blood cell types, including stem cells

YJS

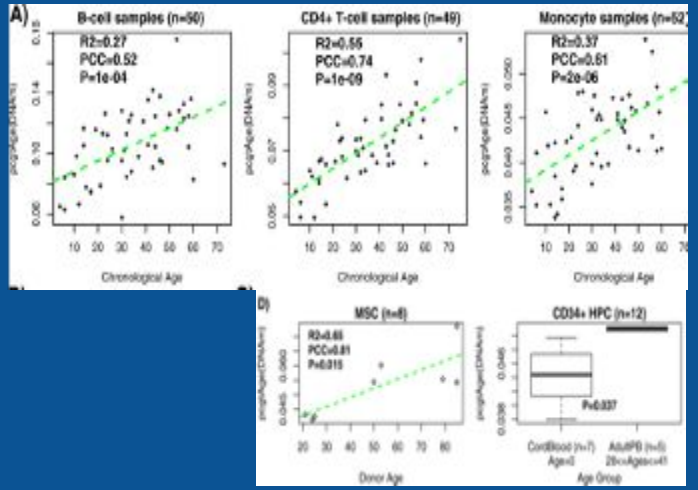
epiTOC predicts age in all blood cell types

pcgtAge vs. chronological age

A. **fraction of 385 PCGT sites are all hypermethylated in the three samples of blood cell type (A)** [21]

epiTOC predicts stem cell age

D. **(Top) correlation of pcgtAge in MSC** [21]
(Bottom) correlation of pcgtAge in HPC [21]

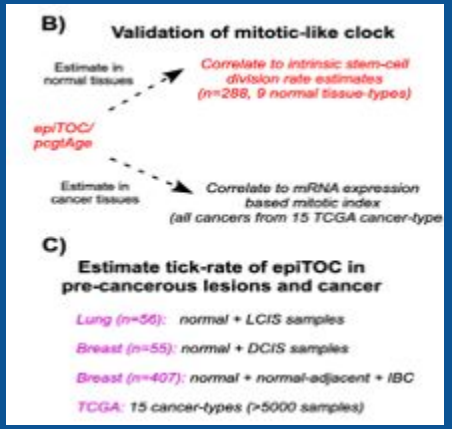


Y axis: pcgtAge (DNAm)
X axis: Donor age

Validation and rate of epiTOC

B. Validation using stem cell division rate & mRNA levels-TCGA [21]

C. See if epiTOC-pctgAge signature is increased in cancer tissue [21]



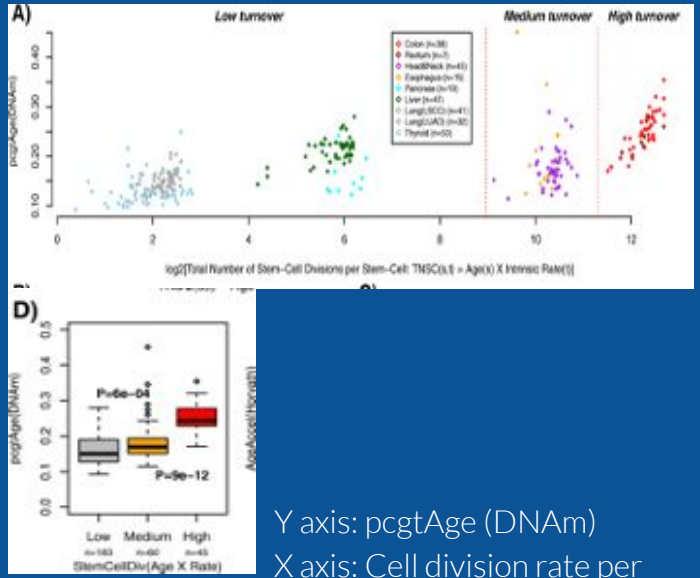
Stem cell rate division

epiTOC can approximate like mitotic-like clock (n=288, 9 different tissue types) [21]

They were able to insure stem cell rate division (Yang et al., (2016) [21]

A. **cells divided by types, grouped into three groups (low, medium, high turnovers)** [21]

D. **different pcgtAge in the three cancer groups**

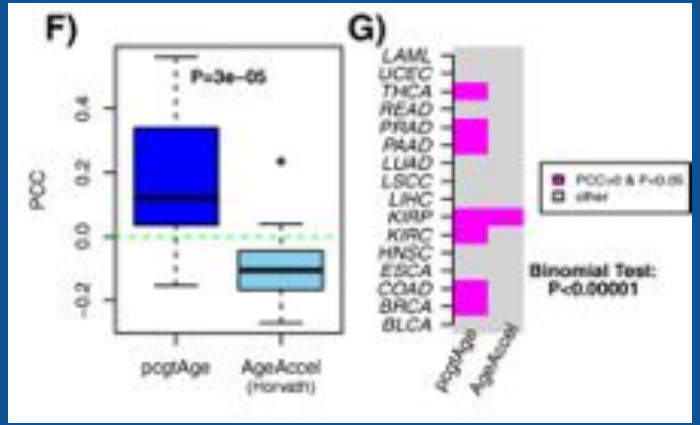


Y axis: pcgtAge (DNAm)
X axis: Cell division rate per stem cell

Increased mRNA levels of proliferation clusters

F. **pcgtAge groups showed higher levels of mRNA expression levels (that is genes that are expressed in tumor cells)(Rhodes et al., 2004) [25]**

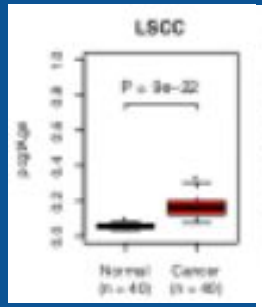
G. **Heatmap: Pink shows the different levels of proteins for the positive pcgtAge groups**



Y axis: Increased mRNA levels of proliferation clusters
X axis: pcgtAge (DNAm)

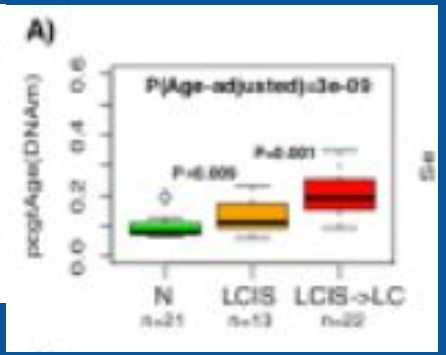
epi-Toc predicts pre-cancerous lesions

A. **Trend in increase in methylation between normal, LCIS ,and LCIS that developed into invasive lung cancer**



LSCC-lung squamous cell carcinoma

Y axis: pcgtAge (DNAm)
X axis: Normal vs. Cancer

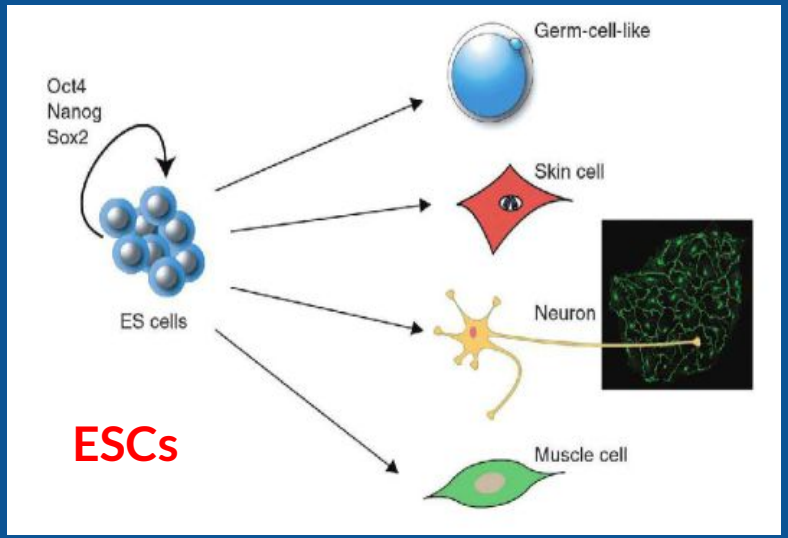


LCIS-lung carcinoma in situ

Y axis: pcgtAge (DNAm)
X axis: Normal, LCIS, LCIS->LC

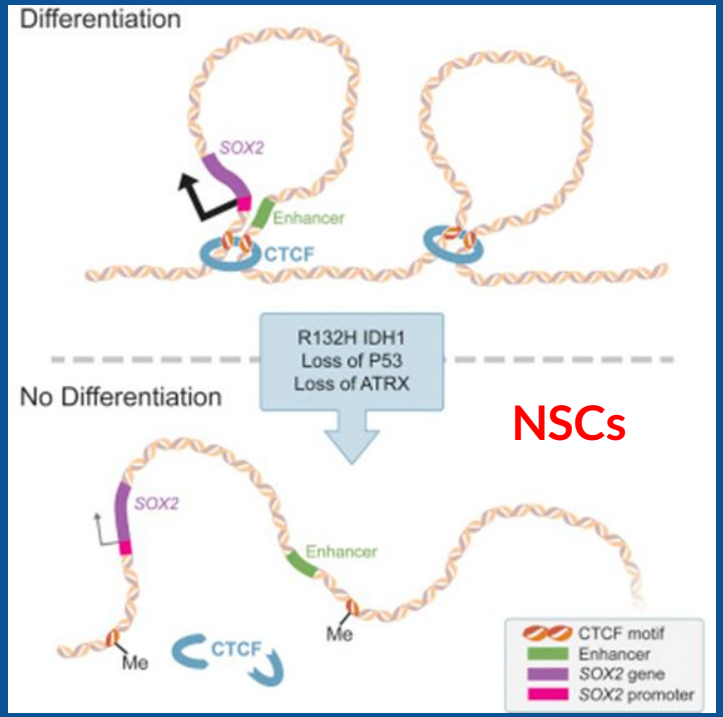
Difficulties - I'm confused? - Give me a Break?!

BJW



↑ Sox2 ↓ESCs differentiation

Repression of SOX2 as an early driver of gliomagenesis [2]



↓ Sox2

↓NSCs differentiation

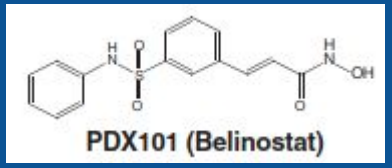
The differentiation block is mediated by transcriptional silencing of SOX2 [2]

Difficulties - Helping or Hurting?

Chemotherapy and radiation can even induce onset of different disease by unmasking late onset of epigenetic alteration.

Second, epigenetic changes might occur in progenitor cells but remain silent without a stress response, as in the case of the action of HSP90 that buffers against phenotypic change or related proteins in *D. melanogaster*[123]. Therefore, stress that is caused by the tumour microenvironment itself (for example, hypoxia) or induced by therapy (for example, cytotoxic drugs or radiation) might unmask the underlying epigenetic heterogeneity within the progenitor cell. In the last case, although the primary tumour is cured, advanced disease might be induced at the same time.

Motivation



Many of these therapeutic strategies aim to induce differentiation of CSCs and to sensitise these cells to chemotherapy, with the ultimate goal of reducing tumor relapse and improving patient (Tol et al. 2017) [12]

Drug	Name	Function/Target	Phase	Disease/Cancer Type
EPZ-5676	Pinometostat	Inhibits DOT1L KMT (H3K79) Activation HoxA9 & Meis1	Phase 1B/2	MLL-fusion leukemia, AML, ALL
Beleodaq	Belinostat	HDACi Class 1 & 2	FDA Approved 2014	Recurrent/refractory cutaneous Peripheral T-cell lymphoma

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