Epigenetics and Human Disease

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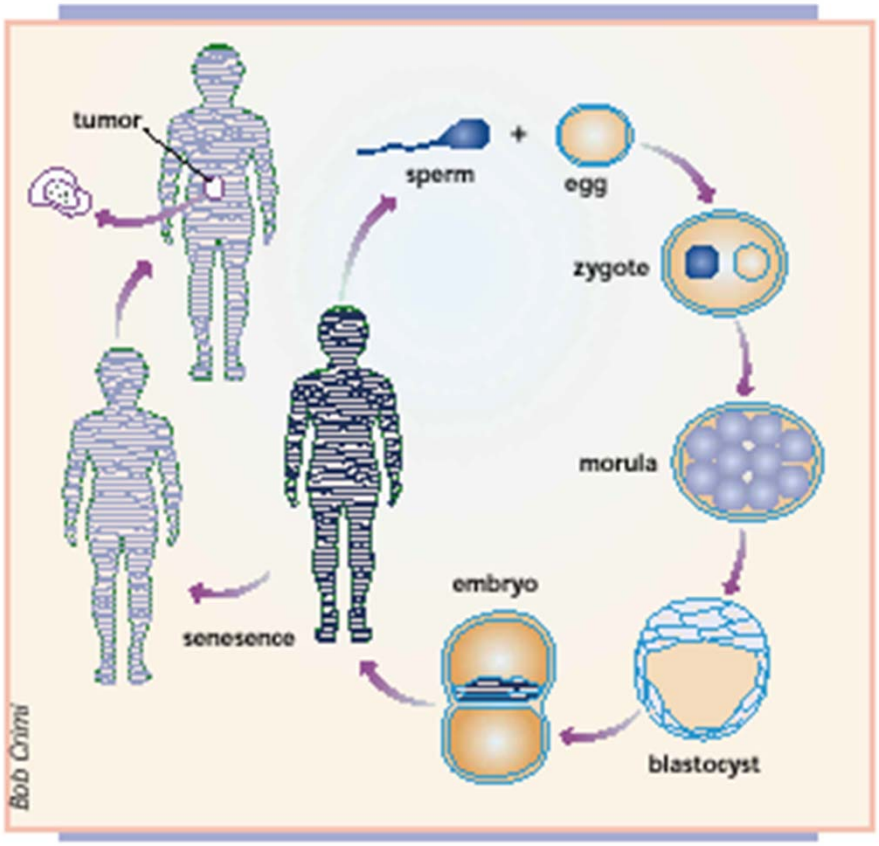
Epigenetics and Human Disease

- Cancer epigenetics
- Epigenetics, stem cells and cancer prevention
- Epigenetics of other common diseases

Life cycle of the epigenome



- Developmental marks
- Stem vs. somatic cell
- Cancer vs. normal cell
- Aged vs. young cell

Feinberg, Nat Genet (01)

Genetic model of cancer

- Cancer caused by mutations in genes
- Good news
  - Predominant mechanism for gatekeeper genes
  - Rare family syndromes: for solid tumors, almost all tumor suppressor genes found by studies of familial cancer
  - Cancer screening for existing tumors
- Bad news
  - Rare in normal cells, even though cancer has a strong genetic component
  - No tests for common cancer risk, in contrast to tests for risk of heart disease

Epigenetic model of cancer

- Cancer caused by epigenetic alterations in genes
- Hypomethylation in 100% of benign and malignant colon tumors
  - Causes chromosomal instability
  - Oncogene activation: H-ras, R-ras, maspin, S100, cyclin D2, 14-3-3σ, MAGE, HPV16, PAX2
- Hypermethylation and chromatin-mediated silencing of TSG
  - RB, VHL, p16, APC, wnt signaling pathway
  - Incipient tests for cancer presence

Epigenetic model of cancer

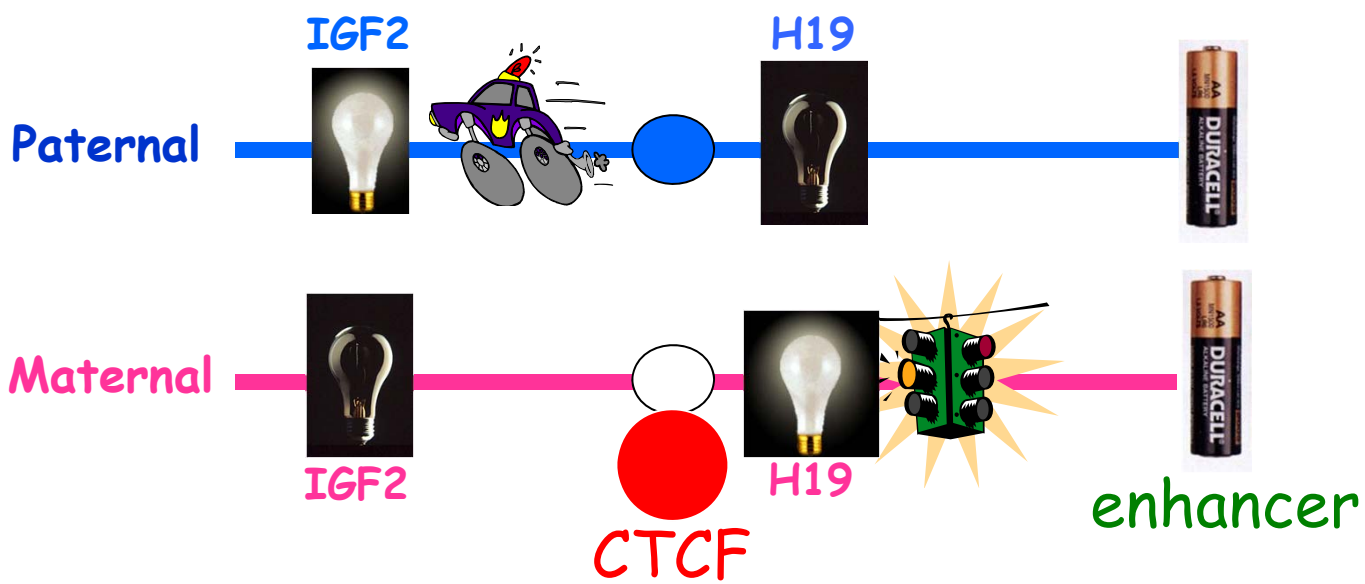
- Chromatin alterations
  - Specific genes: acetylation, lysine methylation of p16
  - Global: Reduction in monoAcH4K16, diMeH4K20, increase in variant histones (CENP-A)
- Epigenetic alterations in *precursor* cells
  - Loss of imprinting (to be discussed)
  - Altered DNA methylation
  - Increased risk of cancer
- May be reversible, unlike genetic changes

Environmental effects on methylation

- Choline/methionine in diet and liver cancer (Poirier)
- MDR1 hypomethylation: drug resistance in AML
- Cadmium inhibits DNMT1
- Arsenic induces ras hypomethylation
- Hypomethylation of HPV16 in cervical cancer progression
- MTHF reductase and colorectal cancer
- Lower CRC with high dietary methionine
- IVF linked to epigenetic disease

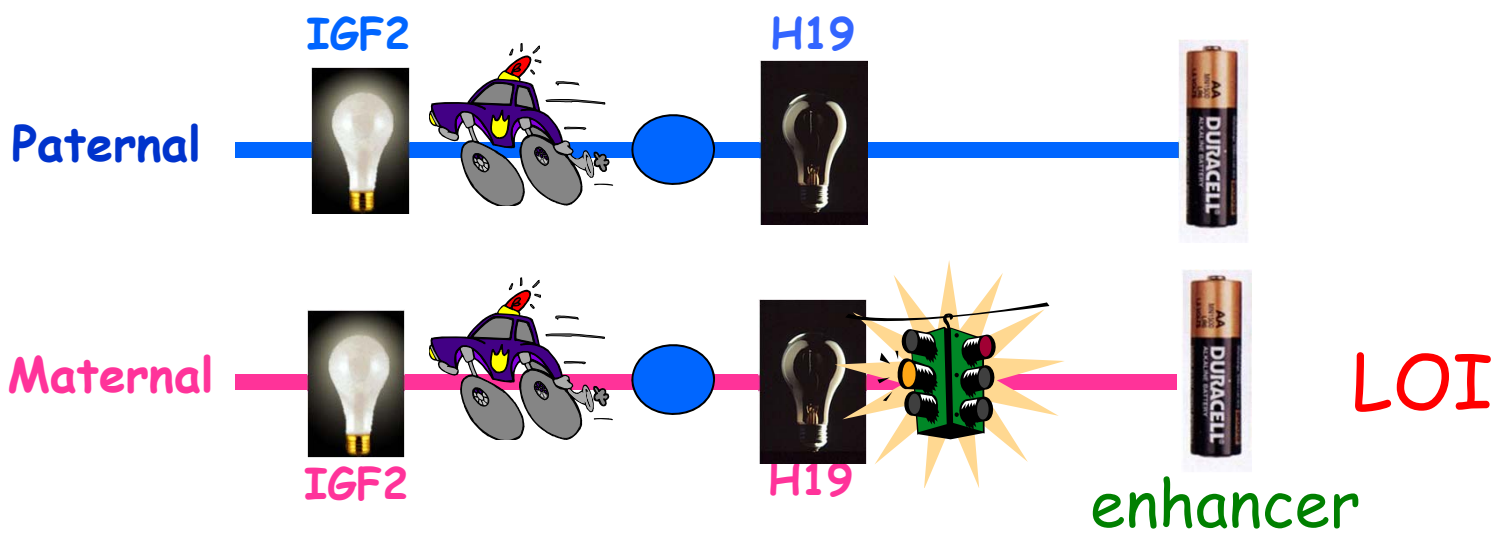
Genomic imprinting

- Cancers show loss of imprinting (LOI) of the insulin-like growth factor II gene (IGF2)



Genomic imprinting

- Cancers show loss of imprinting (LOI) of the insulin-like growth factor II gene (IGF2)



LOI is a common epigenetic variant in the population: associated with cancer risk

	Imprinted N (%)	LOI N (%)	P	OR	P Adj.	OR Adj.
Family history colon cancer						
No	111 (91)	11 (9)	0.004	3.88	0.002	5.15
Yes	36 (72)	14 (28)				
Colonic Neoplasia						
No	100 (93)	7 (6.5)	0.0004	5.41	0.002	4.72
Yes	47 (72)	18 (28)				
Adenomas	43 (77)	13 (23)	0.006	4.28	0.026	3.26
CRC	4 (44)	5 (56)	0.001	16.9	0.0005	21.7

Cui, Cruz-Correa et al, Science (03)

Experimental test of LOI in colorectal cancer

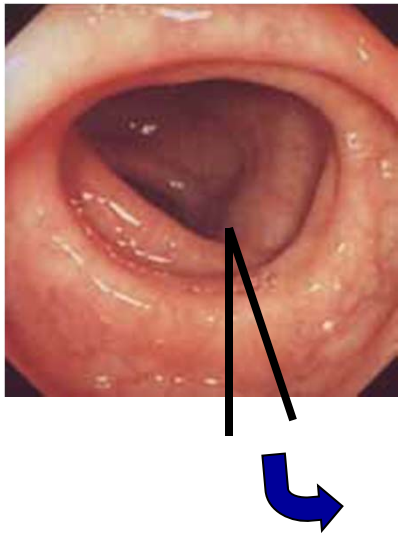
no cancer

no cancer

tumor

more tumors

LOI increases the mouse and human intestinal progenitor cell compartment



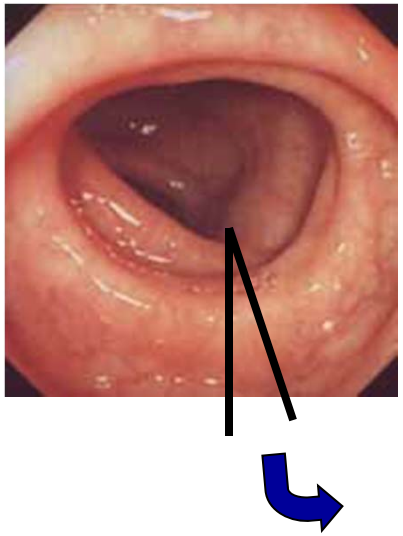
Normal

Differentiated compartment

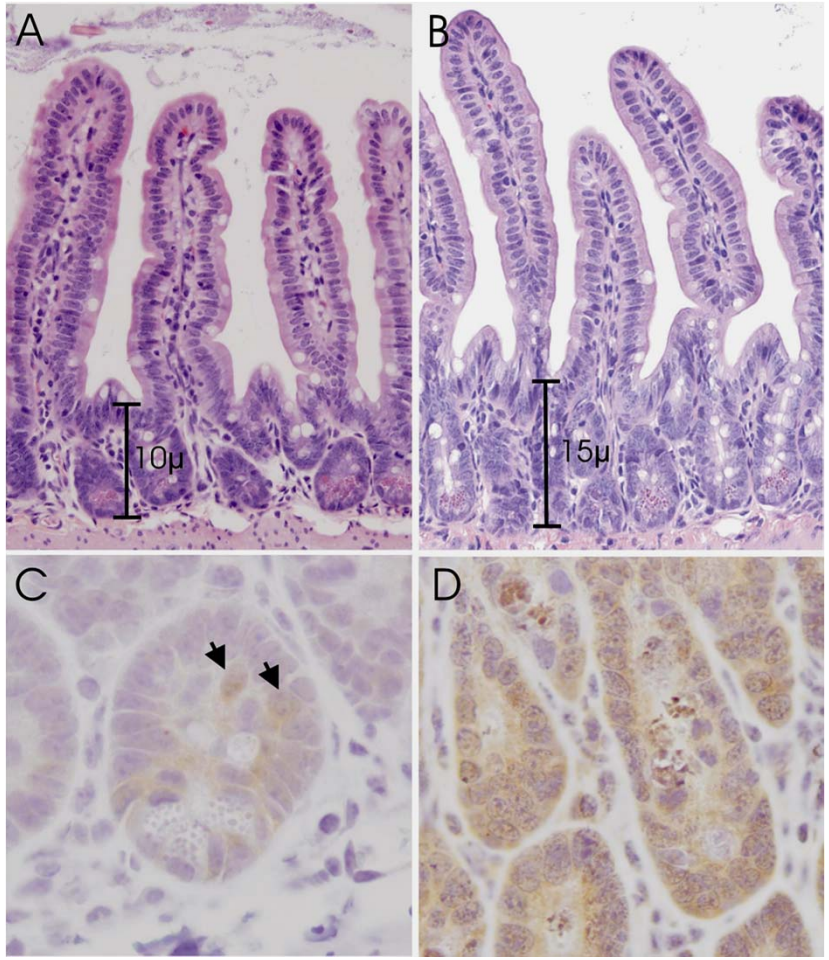
Progenitor cell compartment

Sakatani, et al, *Science* (05)

LOI increases the mouse and human intestinal progenitor cell compartment



Normal LOI



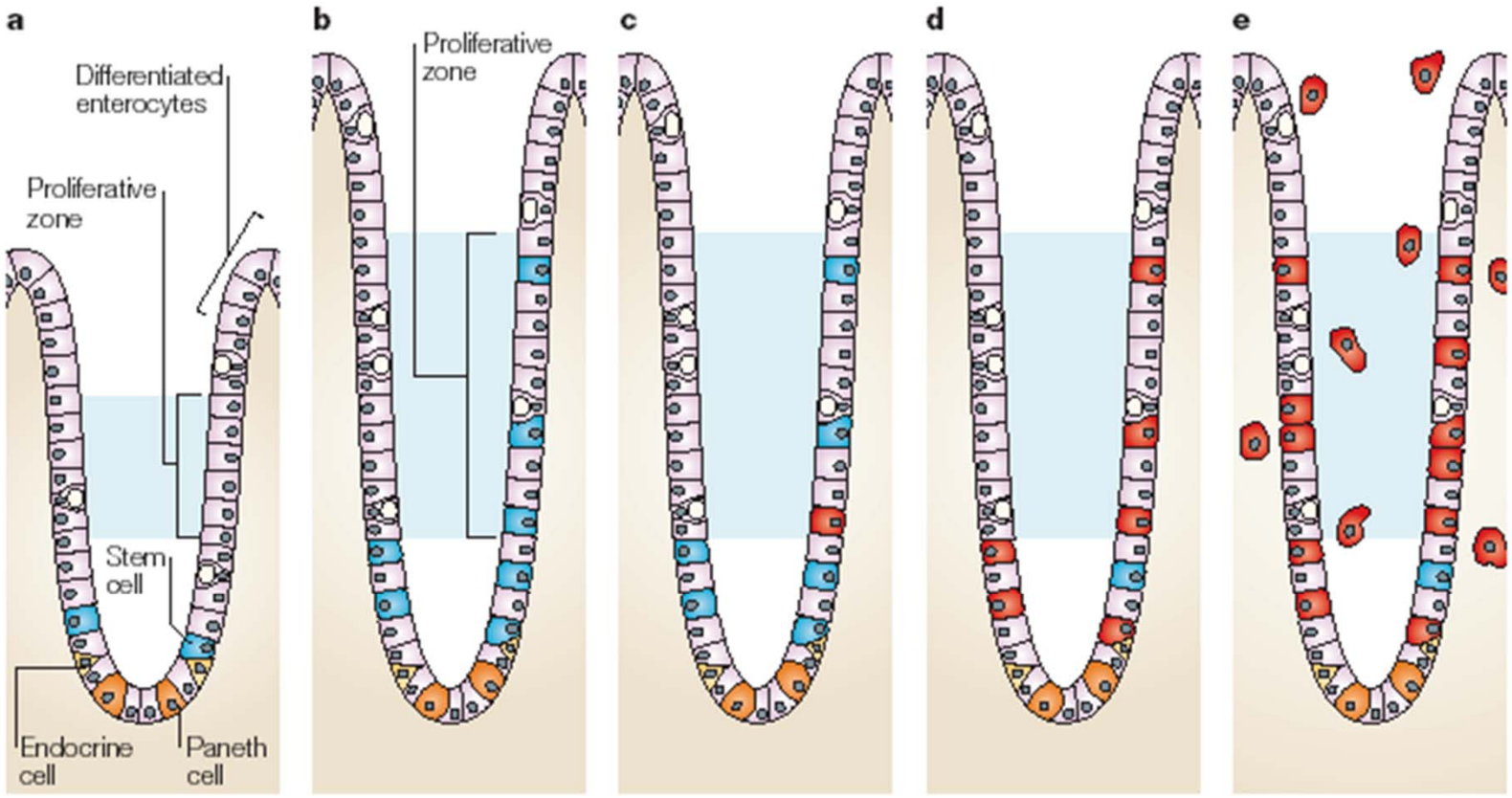
Differentiated compartment

Progenitor cell compartment

Progenitor cell stain (Musashi1)

Sakatani, et al, *Science* (05)

Progenitor cell epigenetic target in colorectal cancer



Nature Reviews | Genetics

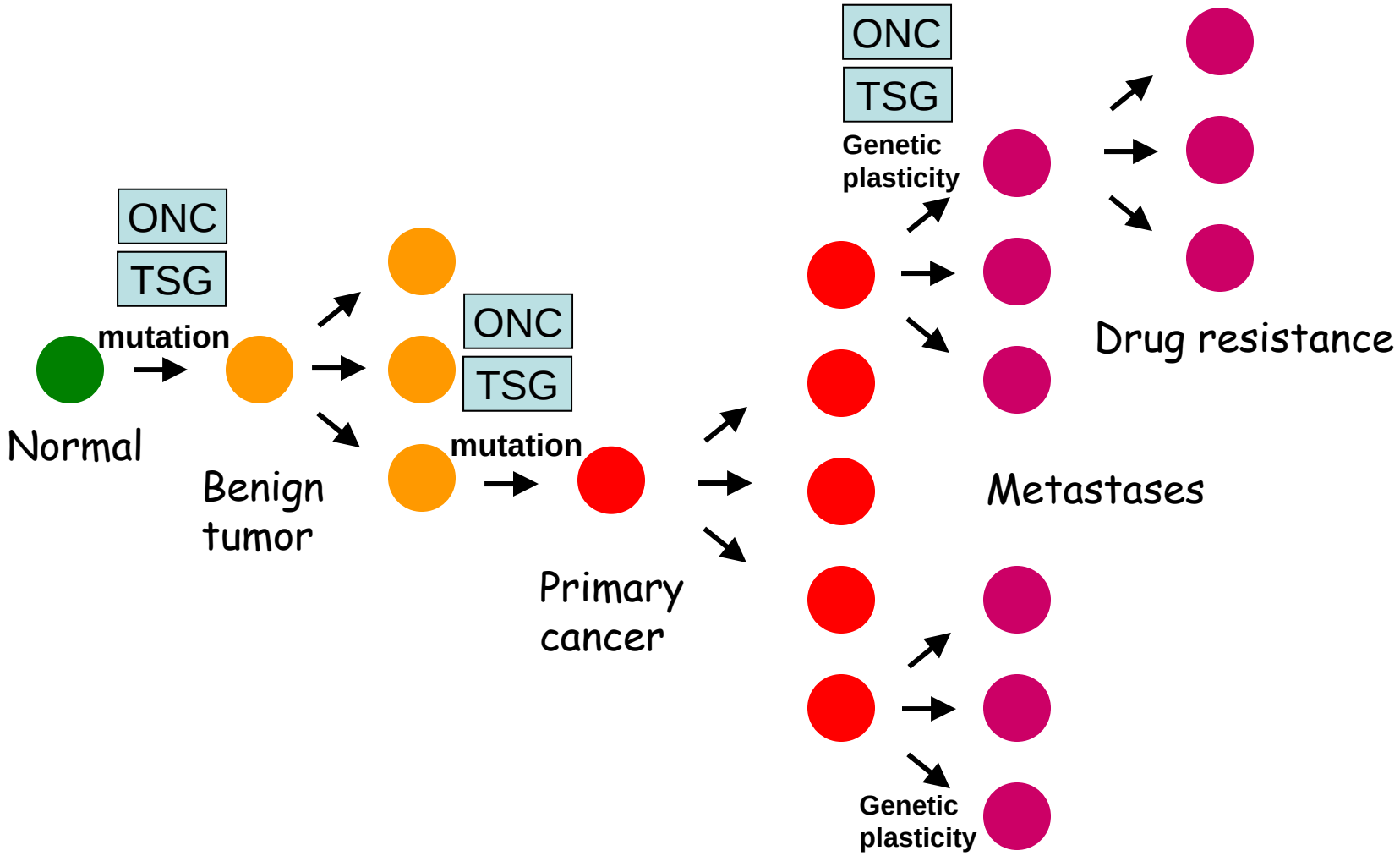
Normal

Epigenetically altered progenitor / microenvironment

Gatekeeper mutation

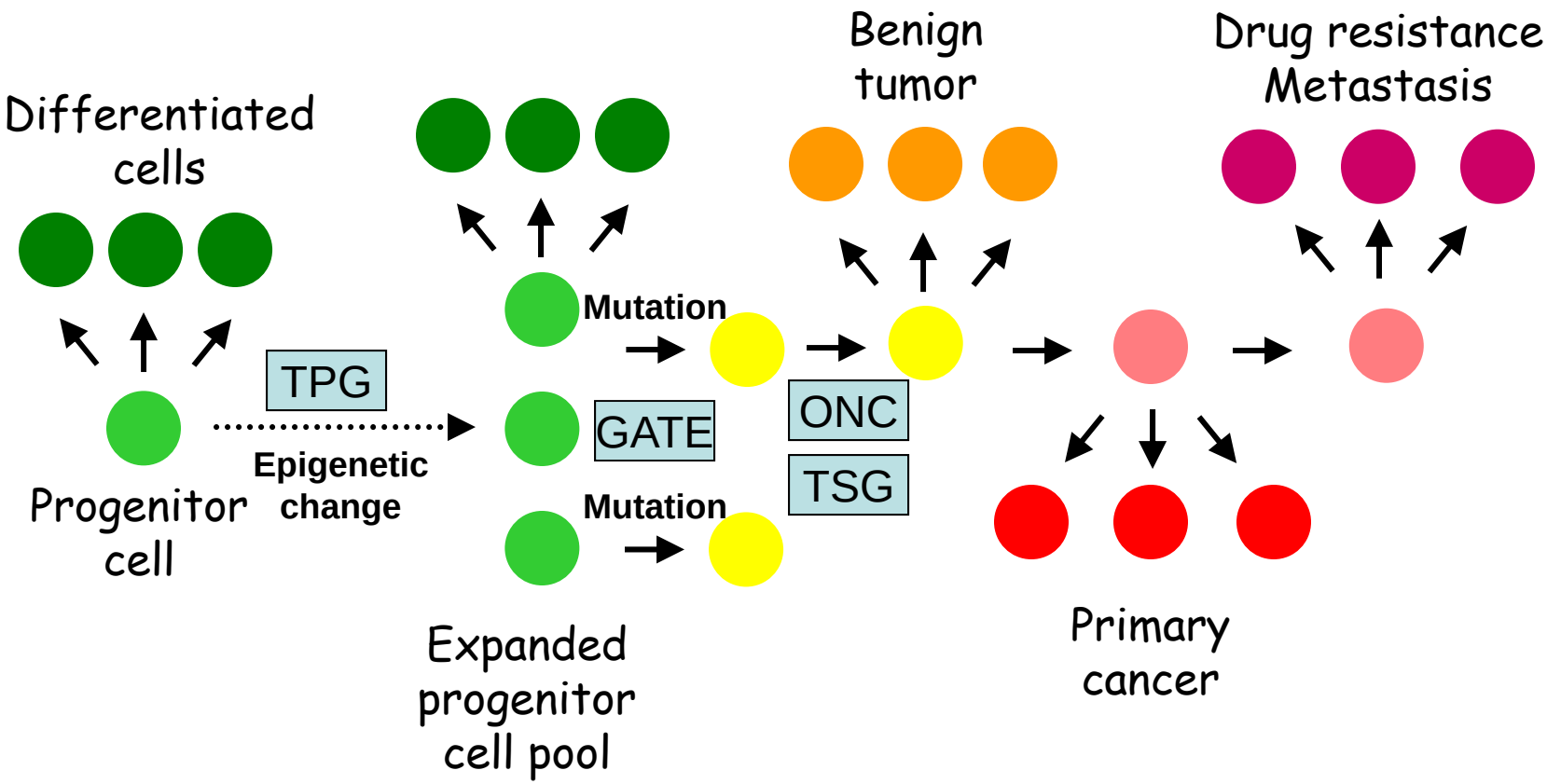
Genetic /epigenetic plasticity

Clonal genetic model of cancer



Feinberg, et al, *Nature Rev Genet* (sub)

Epigenetic progenitor model of cancer



Feinberg, et al, *Nature Rev Genet* (sub)

Epigenetic progenitor model of cancer

- Evidence supporting the model
  - Classic in vitro studies showing reversibility
  - Global epigenetic changes precede mutations in cancer
  - Cloned mouse melanoma nuclei differentiate into normal mice
  - Subpopulation of tumor cells with self-renewal capacity
  - Direct evidence of epigenetically altered precursor cells and microenvironment
- Implications of the model for cancer biology
  - Earliest stages precede benign tumors
  - Link between environmental injury and cancer
  - Drug resistance, metastasis, invasion are latent properties of the precursor cell
  - Late onset of most primary cancers
  - Recurrent primary tumors

Epigenetic progenitor model of cancer

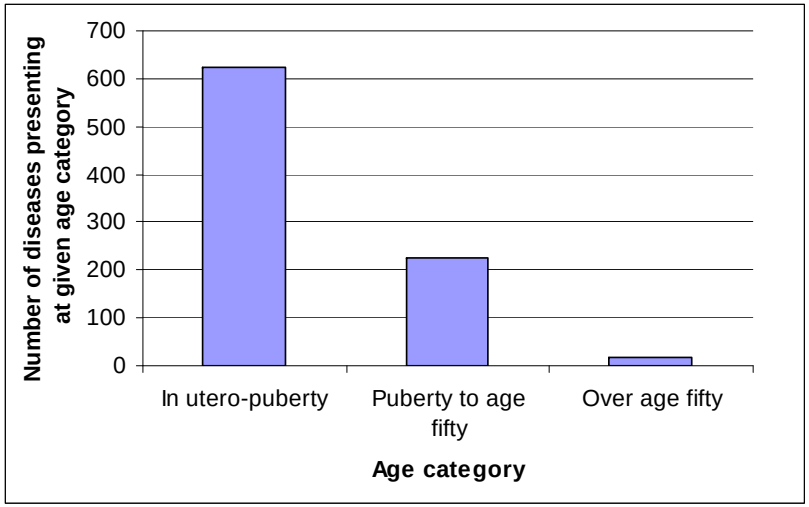
- Implications of the model for human health
  - No improvement in cancer mortality in 50 years (194 per 100,000)
  - Germline genetic changes are rare
  - Epigenetic changes are common
  - Opportunity for epigenetic risk assessment, chemoprevention, and therapy

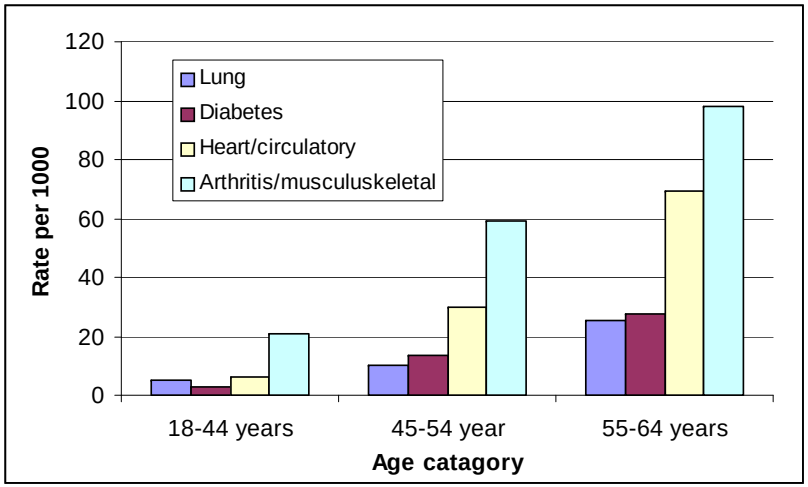
The great question of human genetics:

To what degree does genetic variation contribute to normal phenotypic variation and common human disease?

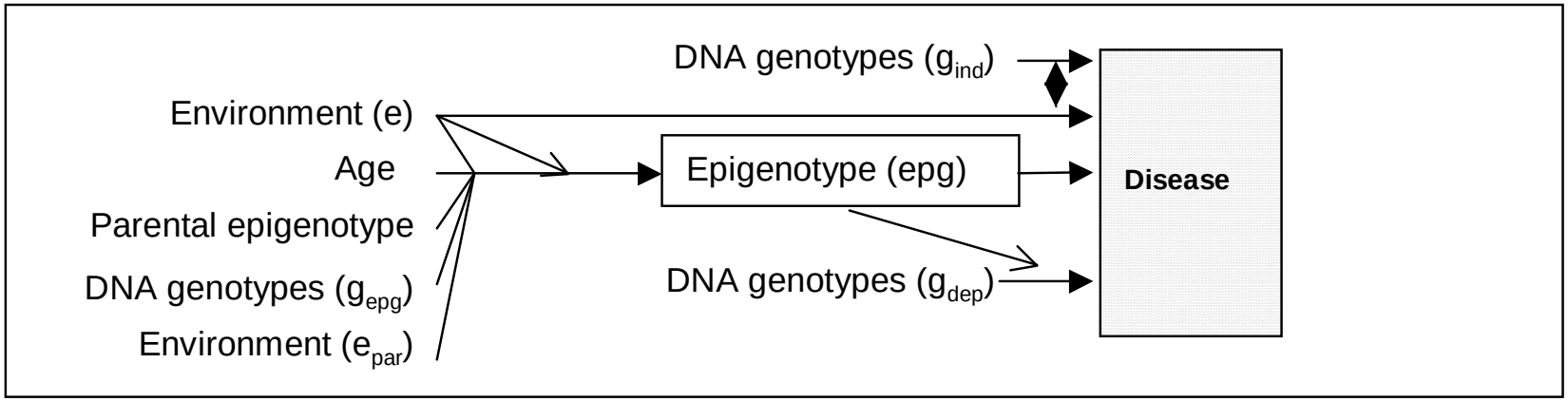
Why might epigenetics also be important in understanding common disease?

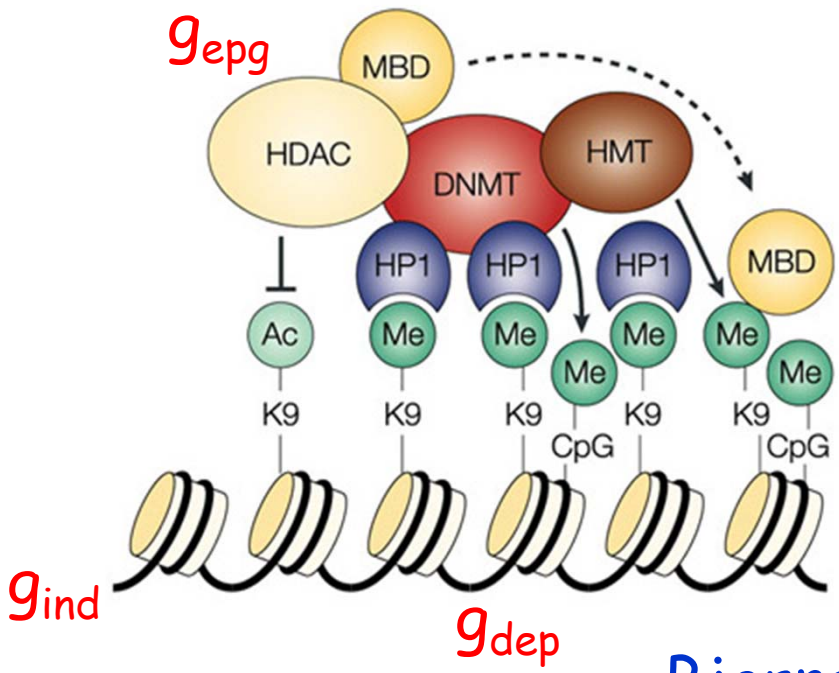
- Epigenome is an important environmental target
- Most common diseases are of adult onset
- The risk and progression increase with age





Where does the epigenotype fit in the picture?

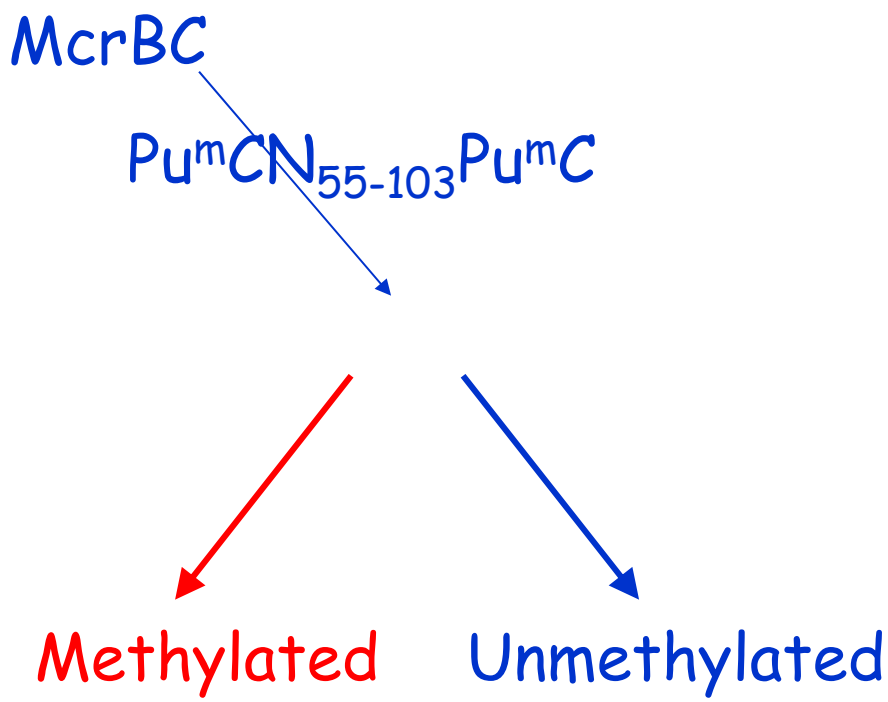




Bjornsson et al, *TIGS* (05)

Epigenomics: High throughput analysis of the epigenetic variation across the whole genome

A glimpse into the human epigenome



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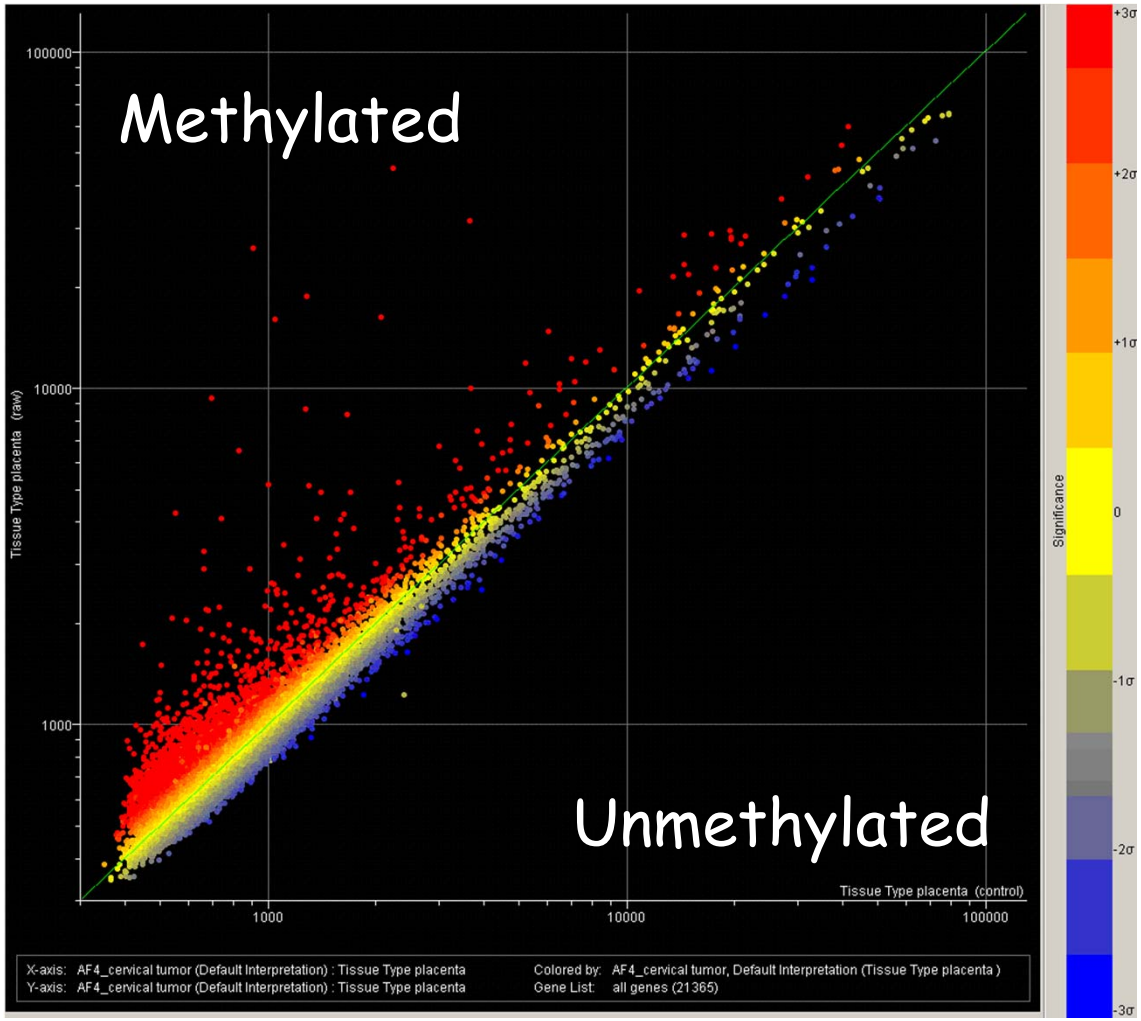
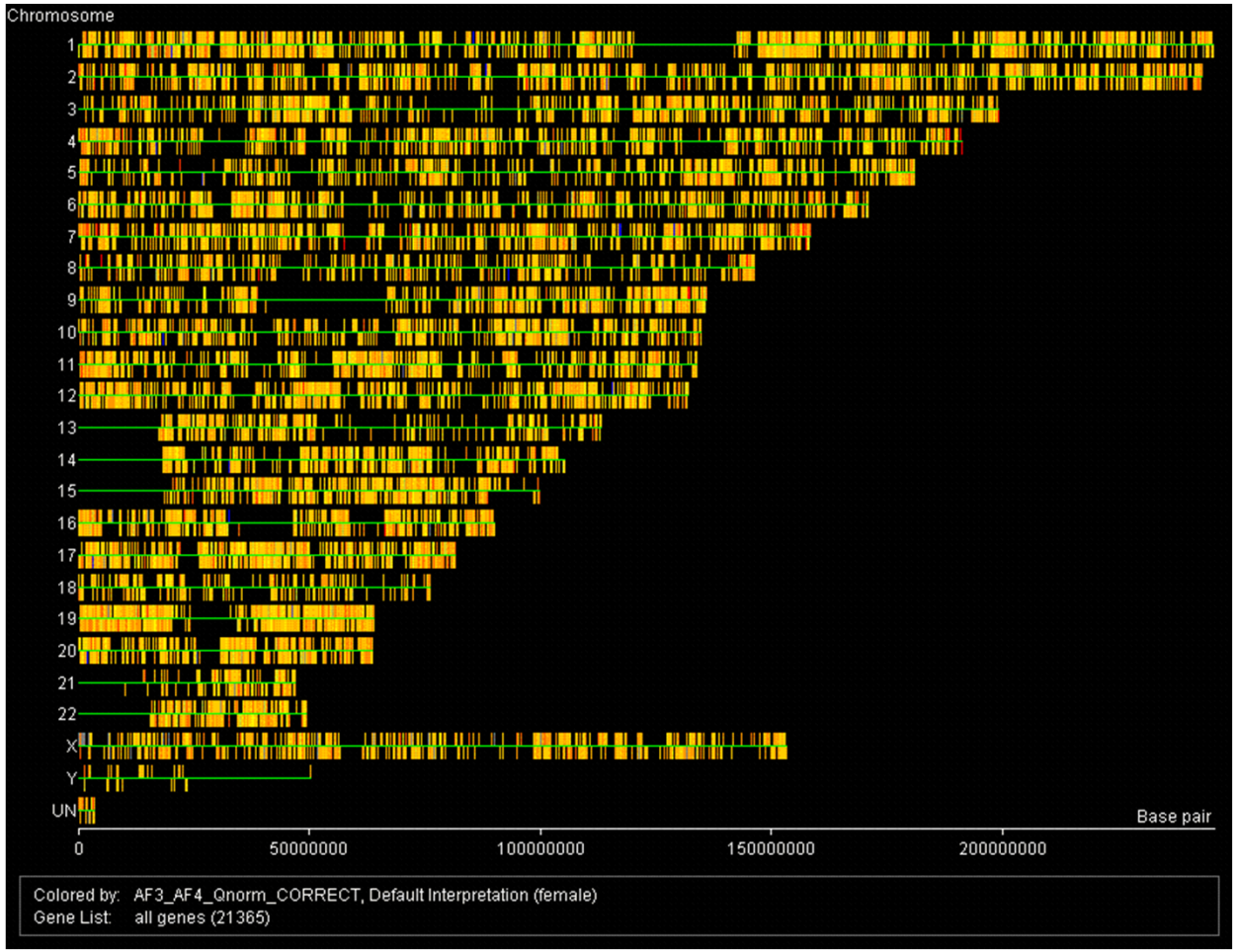


(Feinberg, Jeddeloh, et al)

A glimpse into the human epigenome



Motto of epigenomicists
(borrowed from Galileo Galilei)

Measure what is measurable,
and make measurable what is not so