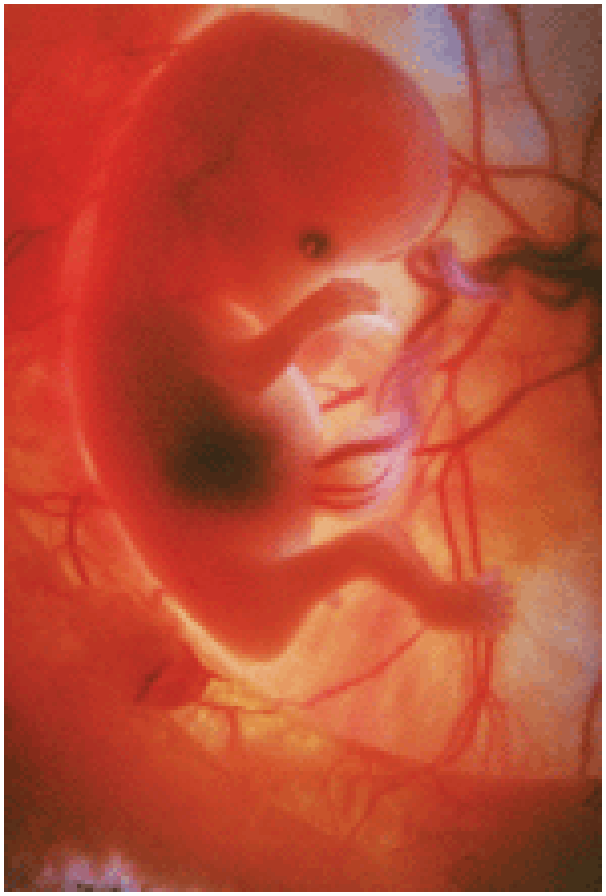
Developmental Reprogramming



Exposure of developing tissues or organs to an adverse stimulus or insult during critical periods of development that can permanently reprogram normal physiological responses in such a way as to give rise to disease later in life

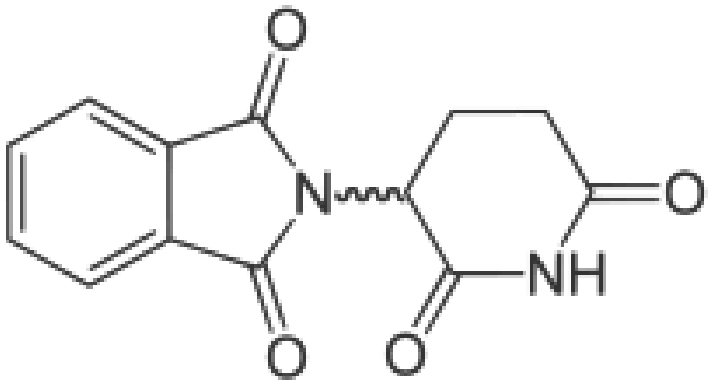
Our Early Life Environment Impacts Us as Adults

What we learned in the 60's

Congenital Abnormalities

- Limb malformations
- Spina bifida
- Neurological deficits

- Thalidomide
- Folate deficiency
- Alcohol



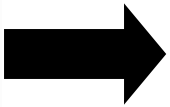
Thalidomide

Our Early Life Environment Impacts Us as Adults

What we learned in the 60's

What we learned in the 80's

Congenital Abnormalities



Physiological "Set-points"

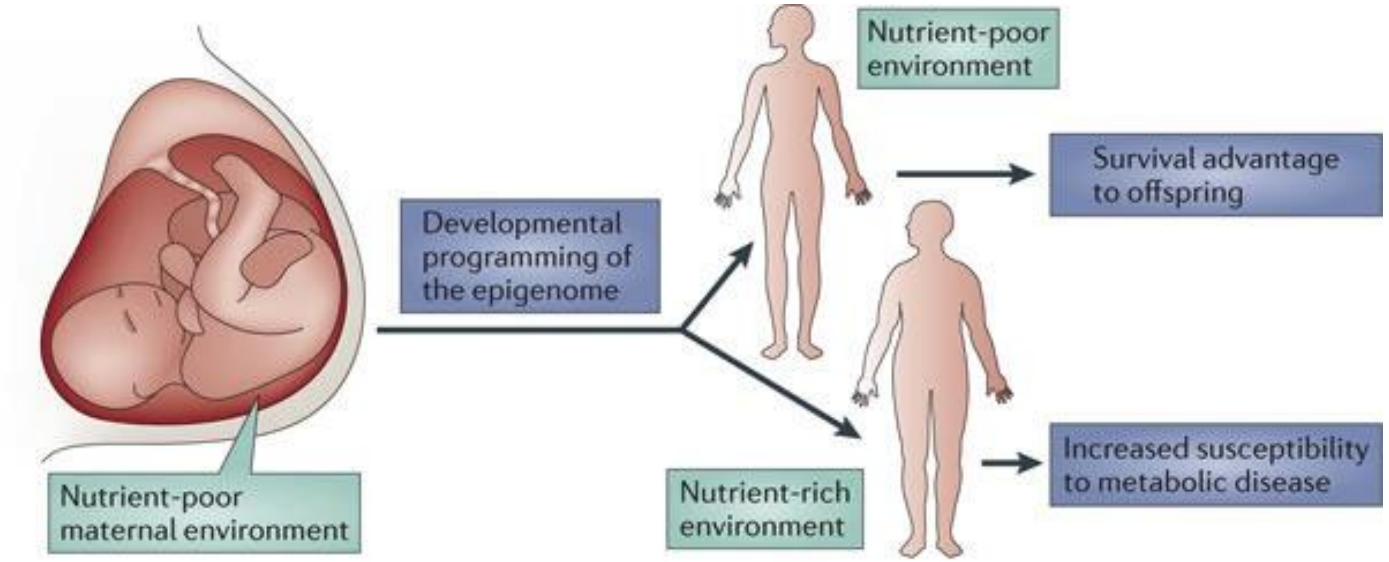
- Limb malformations
- Spina bifida
- Neurological deficits

- Type II Diabetes
- Hypertension
- Obesity

- Thalidomide
- Folate deficiency
- Alcohol

•Fetal Environment in the Womb

Epigenomic Plasticity During Development Allows "Pre-Adaptation" to the Adult Environment



Walker and Ho *Nature Rev Cancer* 2012

- Plasticity of the epigenome during development affords an opportunity for the developing organism to 'pre-adapt' to the future adult environment, which provides a survival advantage.
- However, in settings in which the fetal environment does not match the adult environment — for example, fetal development in a nutrient-poor environment (such as maternal starvation) coupled with a nutrient-rich adult environment — the resulting disconnect between fetal programming and the adult environment can predispose to adult metabolic disease, including obesity and type II diabetes.

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What we learned in the 80's

Physiological "Set-points"

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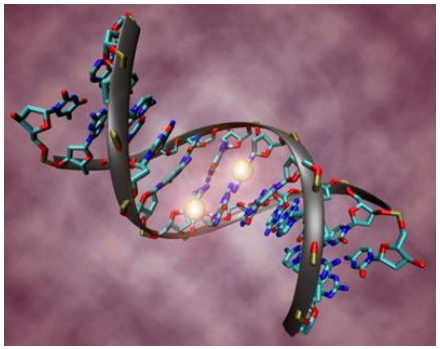
- Obesity

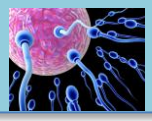
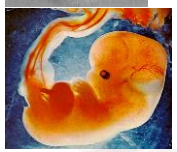
- Fetal Environment in the Womb

What we know in 2014

Molecular (re)Programming



- Chemicals in Our Environment

		What makes these life-stages so sensitive?	Environmental Exposure
Preconception		Genotoxicity and induction of mutations	Paternal Radiation
Childhood • In utero/ Perinatal • Early Childhood • Prepuberty	   	•Developmental reprogramming of the epigenome •Growth promotion via hormones and growth factors leading to expansion of target cell populations and an increase in "at risk" cells	Chemicals that mimic our natural hormones
Adulthood • Puberty • Reproductive years (First full-term pregnancy) • Menopause	 	•Normal (and pathophysiological) tissue remodeling in response to ovarian and other hormones (mammary gland involution after lactation) •Increased susceptibility of proliferating cells to mutations •Immune modulation and escape from immunosurveillance	Cigarette smoke
Postmenopausal		• Changes in levels of circulating hormones (estrogens, adipokines) that promote tumor growth growth	Obesity

Programming the Genome

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TTCTTTCTGTGGTGCTTTACAAAATCTTGAACTTCTGGAATTGATCAAGCAGATAGACG
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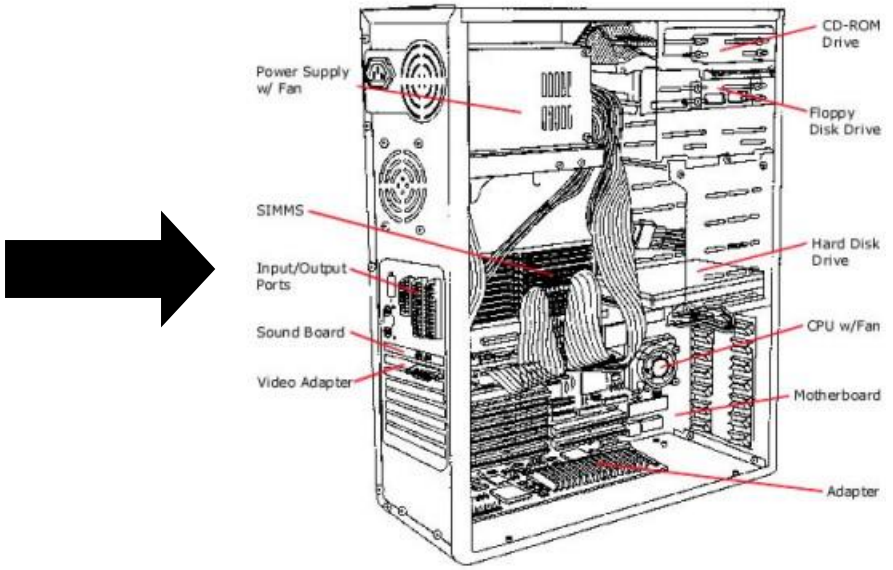
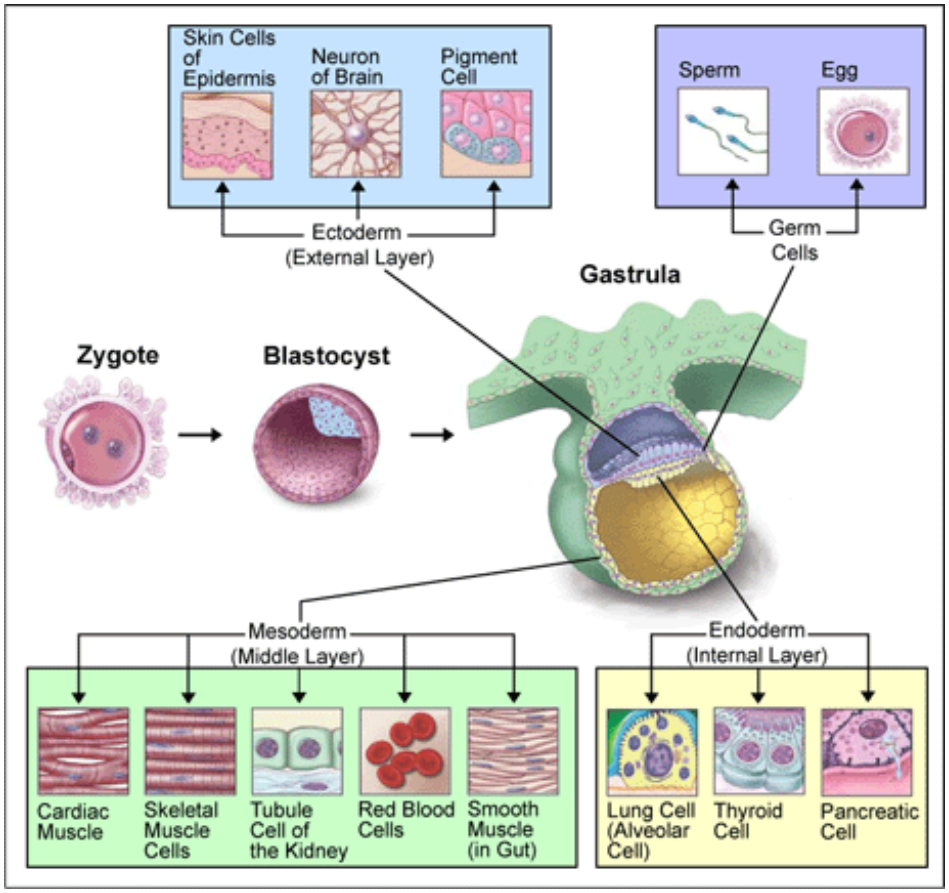


Epigenome = Software (determines how we function)

Fetal and Early Postnatal Development are Critical Periods for Epigenomic "Programming"

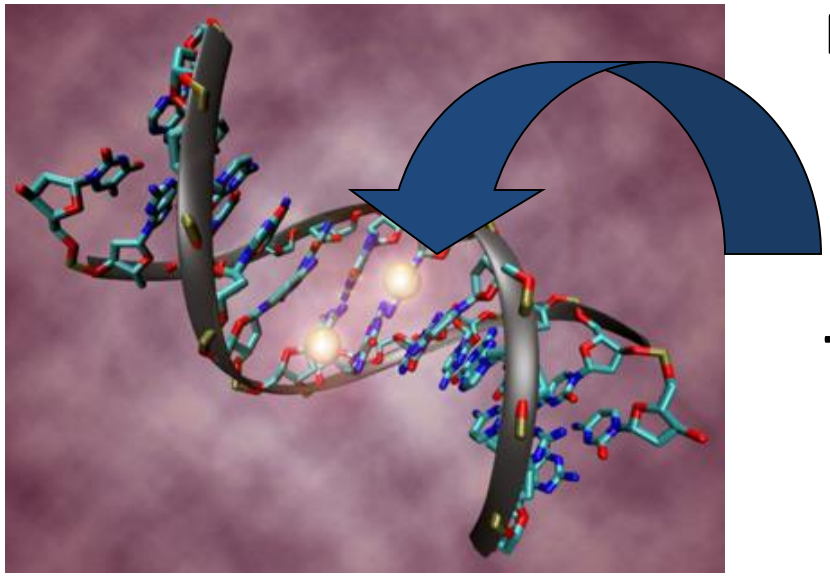


- During development, the genome of cells that make up tissues and organs becomes "programmed" to specify their function in the adult
- Much like when installing new software on a computer, the health of the developing organism depends on a proper "install" of the epigenome
- Disrupting the process during the "install" phase will dramatically alter how the "software" or "programming" functions in the future

Environmental Exposures During Development Can Imprint DNA for Life

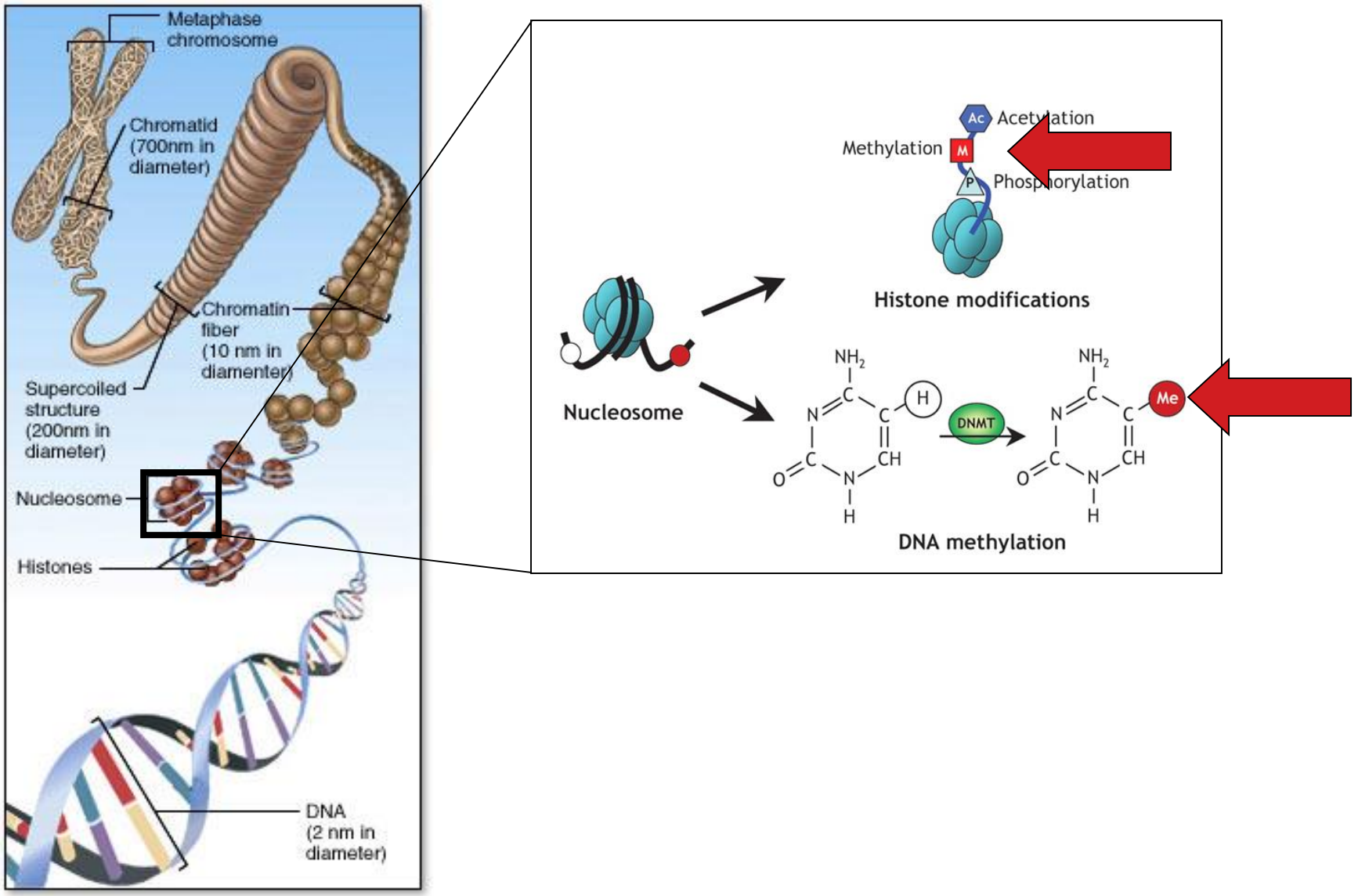
Much like an intruder can leave a fingerprint behind, environmental exposures can leave an imprint on the epigenome

Environmental Exposures During Development Can Imprint DNA for Life

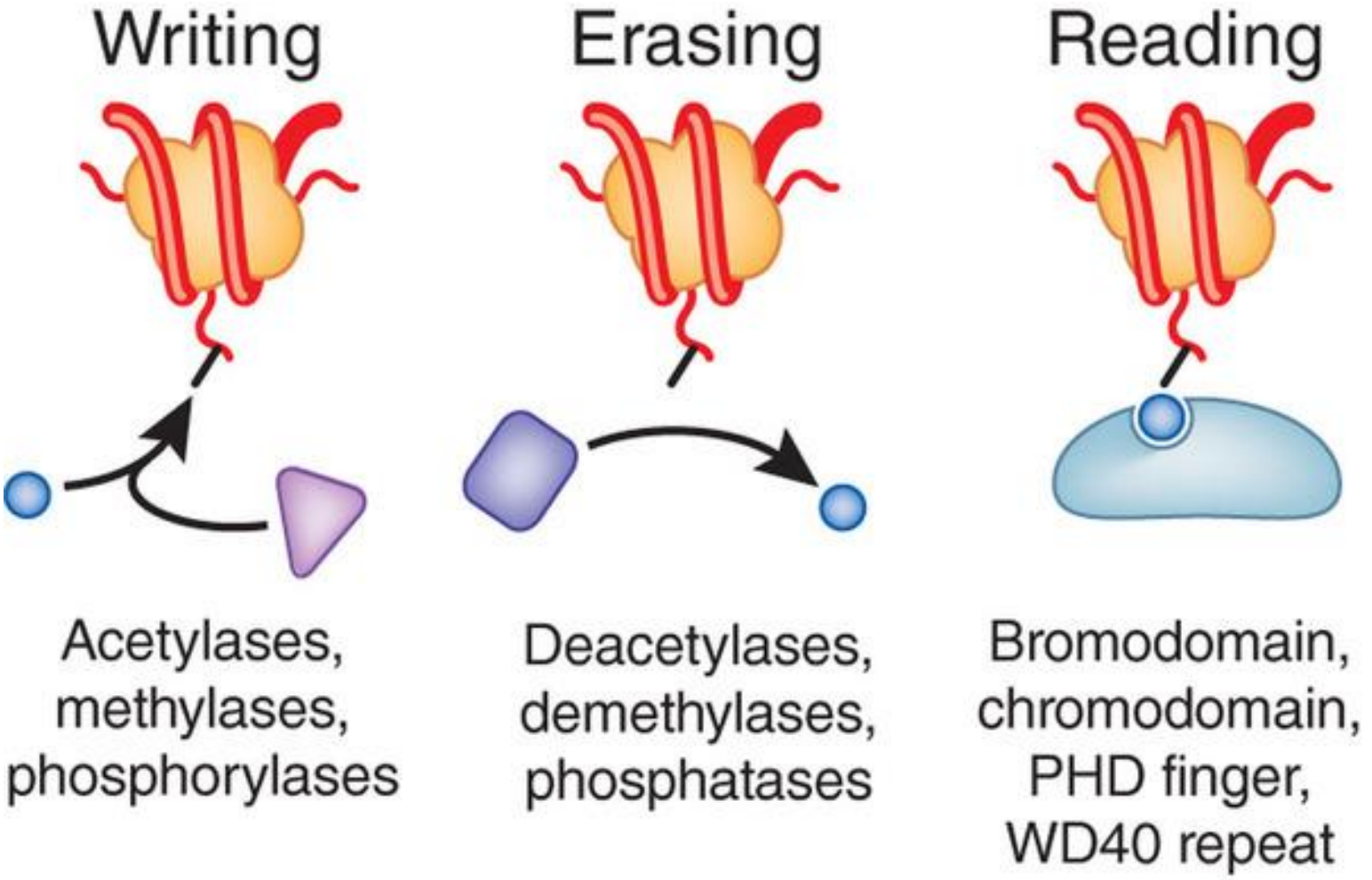


- Much like an intruder can leave a fingerprint behind, environmental exposures can leave an imprint on the epigenome
- These “imprints” are then faithfully copied each time a cell divides, much in the same way as DNA
- In this way, even a short exposure to an environmental agent during development can have life-long effects

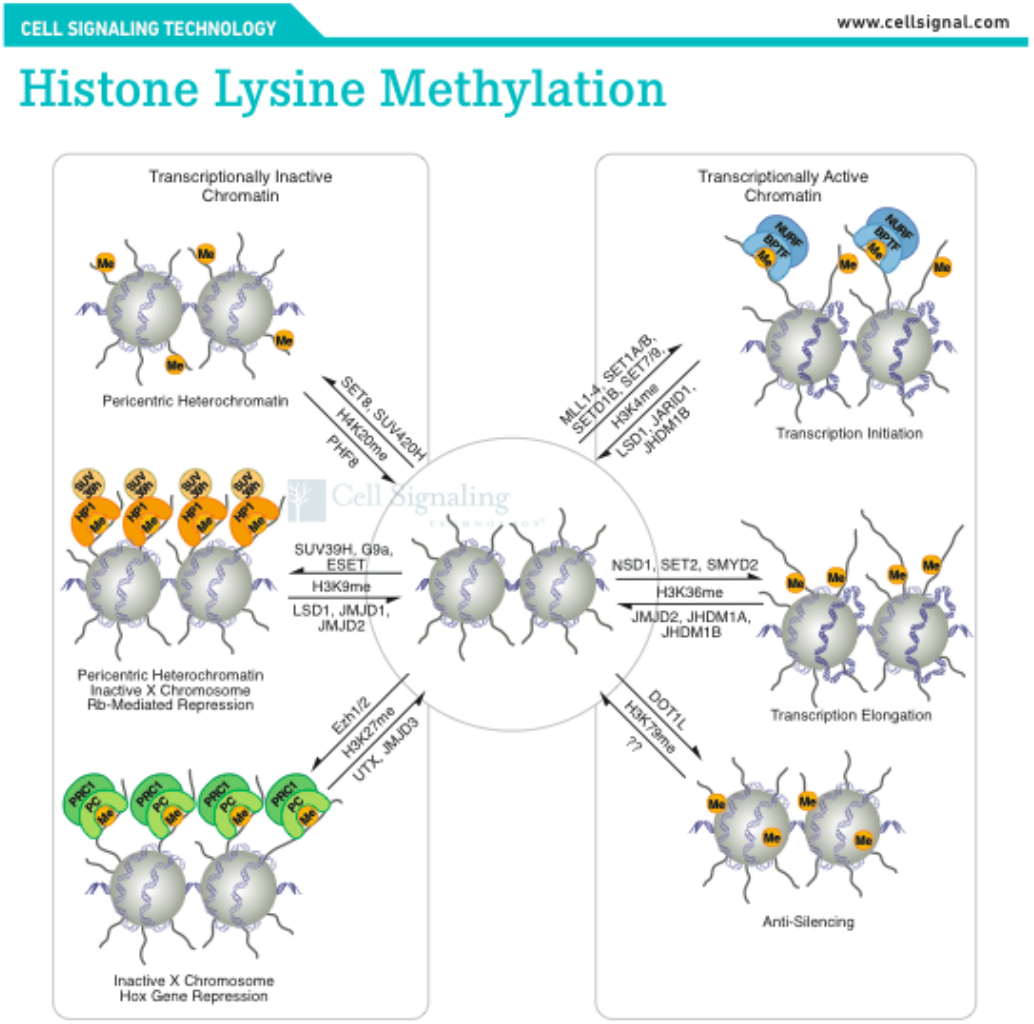
Epigenome as a Target for Developmental (re)Programming



Xenoestrogens Affect the Activity of Epigenetic "Readers, Writers and Erasers"?

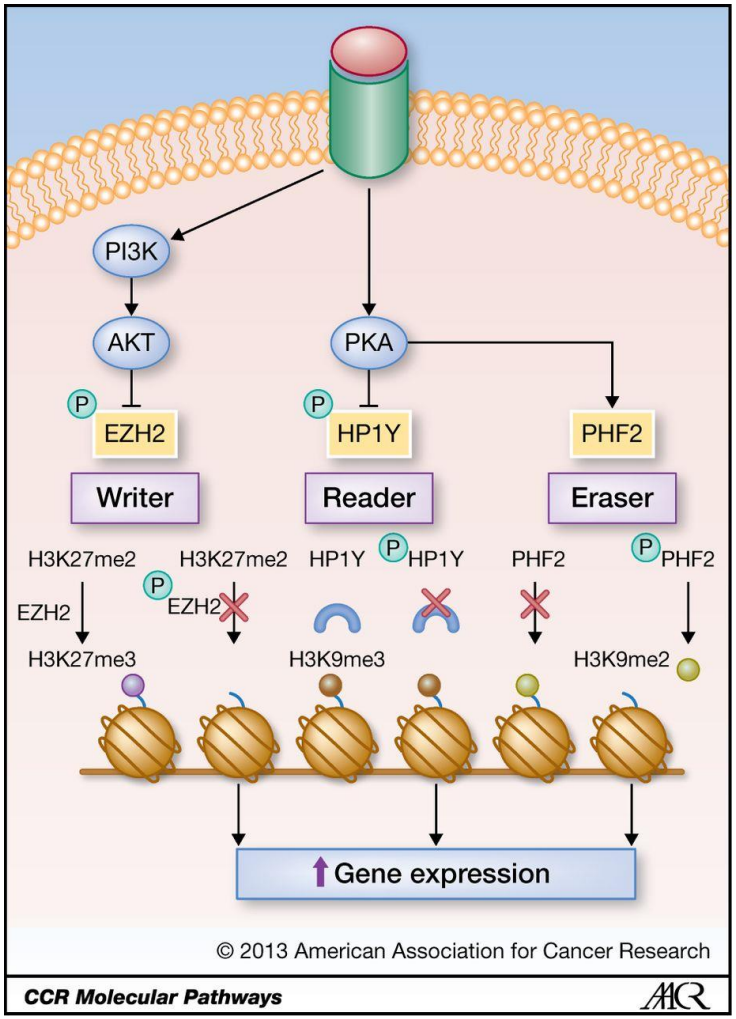


Histone Methylation: Versatility for Epigenomic Plasticity



- We have focused initially on epigenetic histone methyl marks, which can both repress and activate gene expression
- These marks are laid down by histone methyltransferases, such as EZH2 which imparts the repressive H3K27 methyl mark, MLL which imparts the activating H3K4 methyl mark
- Methyl marks are removed by demethylases such as LSD1 and JMJD1
- Various effector proteins then “read” these marks to modulate chromatin conformation/transcription

EDCs Signal to Epigenetic "Readers, Writers and Erasers" to (re)Program the Epigenome

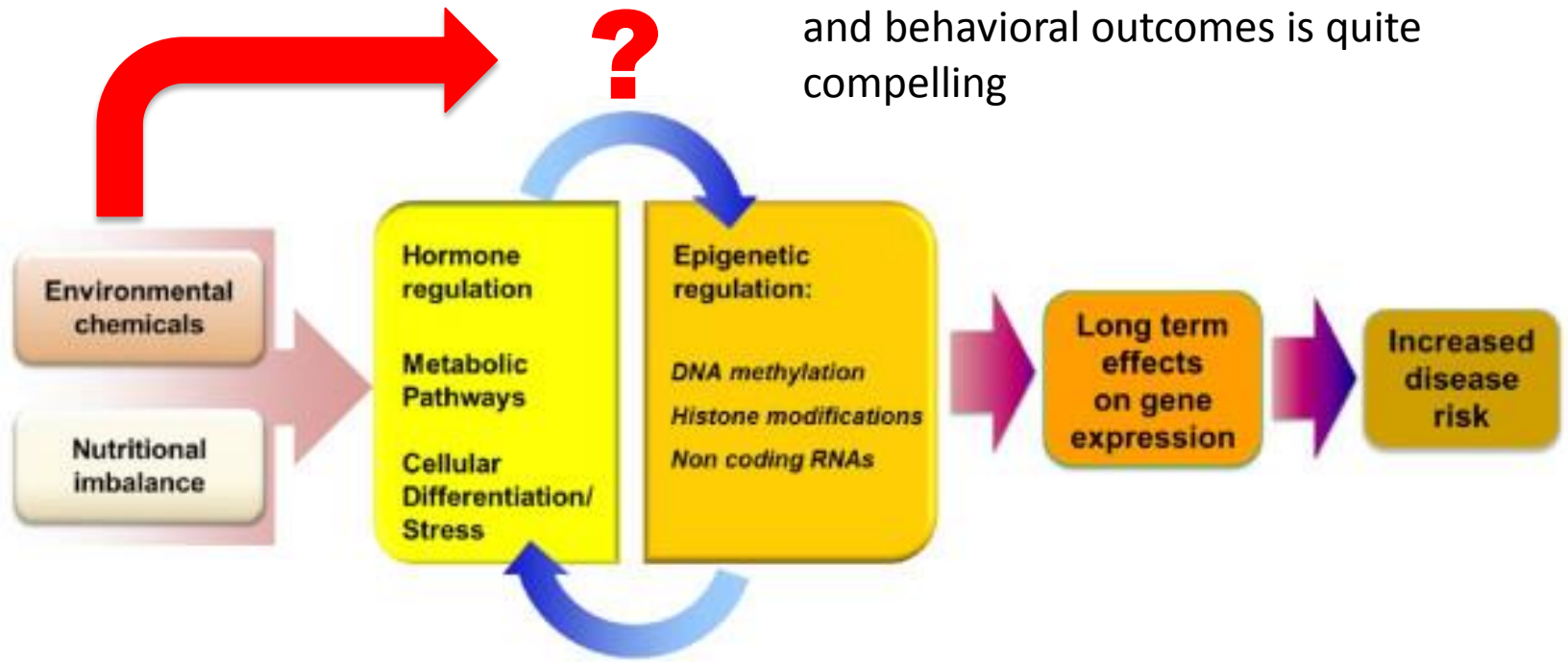


Wong R L Y , and Walker C L Clin Cancer Res 2013

- Activation of nongenomic signaling modulates the activity of epigenetic "readers, writers, and erasers."
- Both endogenous ligands and environmental chemicals bind to NHRs to activate nongenomic signaling.
- Kinases activated by these pathways phosphorylate epigenetic programmers to modulate their activity

Our Early Life Environment Impacts Us as Adults

Evidence for epigenetic (re)programming by environmental exposures to increase susceptibility to metabolic (e.g. obesity, diabetes) and cardiovascular diseases, cancer, neurological, reproductive and and behavioral outcomes is quite compelling



Developmental Origins of non-communicable disease: Implications for research and public health
Barouki, Glukman, Grandjean and Heindel *Environ Health* 2012