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

- Thalidomide
- Folate deficiency
- Alcohol
Our Early Life Environment Impacts Us as Adults

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What we learned in the 80’s
- Physiological “Set-points”
  - Type II Diabetes
  - Hypertension
  - Obesity
- Fetal Environment in the Womb
Epigenomic Plasticity During Development Allows “Pre-Adaptation” to the Adult Environment

- 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.
Our Early Life Environment Impacts Us as Adults

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What we know in 2014
- Molecular (re)Programming
  - Chemicals in Our Environment
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<th>Life Stage</th>
<th>Events</th>
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<td>Genotoxicity and induction of mutations</td>
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<td>• Early Childhood</td>
<td>• Growth promotion via hormones and growth factors leading to expansion of target cell populations and an increase in “at risk” cells</td>
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<td>• Prepuberty</td>
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<td>Adulthood</td>
<td>• Puberty</td>
<td>• Normal (and pathophysiological) tissue remodeling in response to ovarian and other hormones (mammary gland involution after lactation)</td>
<td>Cigarette smoke</td>
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<td>• Reproductive years (First full-term pregnancy)</td>
<td>• Increased susceptibility of proliferating cells to mutations</td>
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<td>• Menopause</td>
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<td>• Changes in levels of circulating hormones (estrogens, adipokines)</td>
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**Programming the Genome**

**DNA = Hardware (we come hardwired)**

**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”? 

- **Writing**: Acetylases, methylases, phosphorylases
- **Erasing**: Deacetylases, demethylases, phosphatases
- **Reading**: Bromodomain, chromodomain, PHD finger, WD40 repeat
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

- 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 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