Developmental Basis of Disease: A New Paradigm in Environmental Health Sciences

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Background I

- Barker hypothesis proposed that abnormal developmental nutrition could lead to increased susceptibility to disease later in life.

- We have always been aware of the acutely sensitive nature of the developmental period to environmental perturbations.
  - The developing organism (fetus and neonate) is extremely sensitive to perturbation by chemicals because....
    - Tissues/organs forming, lack of DNA repair, poor liver metabolism, developing immune system, lack of blood/brain barrier, ↑ metabolic rate
  - However until recently the focus was on
    - death,
    - birth defects,
    - low birth wts as the result of developmental exposures.
    - Scientists talked about functional changes but no one knew
    - how to measure them.
Background II

- The breakthrough came with “omics technology

- This allowed one to “see” functional changes: where outwardly everything looked normal but at the gene expression and proteomics level there were abnormalities (the tissue was functionally abnormal).

- It was soon discovered that low environmentally relevant doses of environmental chemicals could cause “functional changes” without any of the other teratology endpoints.

- These data led the developmental basis of disease paradigm focusing on environmental exposures and not just poor nutrition.
Developmental Basis of Disease; Environmental Exposure Paradigm Features

- Developmental exposure (in utero and neonatal) can lead to increased susceptibility to disease.
- Susceptibility to disease persists long after the exposure is gone...even decades later.
- The toxicant-induced responses are most likely the result of altered gene expression or altered protein regulation (functional change).
- This functional change or aberrant developmental programming, permanently alters gland, organ or system potential.

- HARM IS DISPROPORTIONATE TO DOSE
How can it be that developmental exposures can cause effects that only get expressed long after the exposure?
Epigenetic Alterations: The Molecular “Imprint” Made by Developmental Programming as a Result of Environmental Exposures

• The effects of developmental exposures persisted because altered epigenetic signaling (developmental programming) persisted.
  – DNA methylation of CpG islands
  – Chromatin changes/remodeling

• The developmental time period is the most sensitive to epigenetic alterations in gene expression that then persist throughout life.

• Developmental exposures (along with nutrition, stress, infections) alter epigenetic marks which lead to functional changes which lead to abnormal tissues which lead to disease later in life…..
Animal data support a role for developmental exposures for all of these important human diseases

- Reproductive/Endocrine
  - Breast/prostate cancer
  - Endometriosis
  - Polycystic ovary syndrome
  - Fertility
  - Diabetes/metabolic syndrome
  - Puberty
  - Obesity

- Brain/Nervous System
  - Alzheimer's disease
  - Parkinson’s disease
  - ADHD/learning disabilities

- Pulmonocardovascular
  - Atherosclerosis
  - Asthma
  - Chronic obstructive pulmonary disease
  - Heart disease/hypertension

- Immune/Autoimmune
  - Systemic/tissue specific autoimmune disease
  - Immunosuppression
Animal Data Suggest---Transgenenerational or Gametic Epigenetic Inheritance

- Preliminary data suggests that developmental exposure at the time of germ cell development and erasure of epigenetic marks can lead to “carry over” of altered epigenetic programming across generations (must show effects across 3 generations).

- If true, then what your mother was exposed to during pregnancy can affect your health as well as your children’s health.

- Huge potential impact
The Developmental Basis of Disease: A New Paradigm

• It changes focus from adults to development for the cause of disease.

• It focuses on the perinatal period as a window of opportunity for disease prevention.

• It changes the focus from curing a disease to prevention and intervention strategies to reduce disease incidence.

• It provides an “imprint” left by developmental programming such as altered methyl marks that may be useful for identification of exposed individuals and as a biomarker for disease susceptibility.
Questions arising from Epigenetics and a New Paradigm for Complex Disease

– What changes are occurring and when?
– Are they correlative or causative?
– What are the most sensitive life stages?
– What tools and approaches are needed to prove the relationship?
– Can epigenetic changes be used as biomarkers of exposure? Disease susceptibility? Early Response?
– What are the implications for clinical practice? Public Health Practices? regulatory decision makers?
– What are the implications for disease prevention in this generation and the next?