Obesogens, Stem Cells and the Maternal Programming of Obesity

Bruce Blumberg, Ph.D.
Department of Developmental and Cell Biology
Department of Pharmaceutical Sciences
Developmental Biology Center
University of California, Irvine
The Worldwide Obesity Epidemic

- 34% of the US population are clinically obese (BMI > 30)
  - Double worldwide average (Flegal et al. JAMA 2010;303:235-241)

- 68% are overweight (BMI > 25) - 86% estimated by 2020

- Obesity accounts for 8% of healthcare costs in Western Countries
  - $75 billion annually in US (2005), $147 billion (2009)

- Obesity is associated with “metabolic syndrome” -> type 2 diabetes and cardiovascular disease
  - Central (abdominal obesity)
  - Atherogenic dyslipidemia (high triglycerides, high LDL, low HDL)
  - Hypertension
  - Insulin resistance
  - Prothrombotic state
  - Pro-inflammatory state (elevated CRP)
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
How does obesity occur?

- Prevailing wisdom - “couch potato syndrome”
  - Positive energy balance, i.e., too much food, too little exercise
- Are there other factors in obesity?
  - Stress (elevated glucocorticoids)
  - Inadequate sleep (stress?)
  - “Thrifty” genes which evolved to make the most of scarce calories
  - Viruses, gut microbes, SNPs
- What about role of prenatal nutrition or in utero experience?
  - Southampton studies
  - Maternal smoking decreases birth weight and increases obesity
- What about the role of industrial chemicals in rise of obesity?
  - Baillie-Hamilton (2002) postulated a role for chemical toxins
  - Obesity epidemic roughly correlates with a marked increase in the use of chemicals (plastics, pesticides, etc.)
- Many chemicals have effects on the endocrine system
Hormonal control of weight

- **Hormonal control of appetite and metabolism**
  - Leptin, adiponectin, ghrelin are key players
  - Leptin, adiponectin - adipocytes
  - Grehlin - stomach
  - Thyroid hormone/receptor
    - Sets basal metabolic rate

- **Hormonal control of fat cell development and lipid balance**
  - Regulated through nuclear hormone receptors RXR, PPARγ
  - PPARγ - master regulator of fat cell development
    - increased fat cell differentiation
    - Increased fat storage in existing cells
    - Increased insulin sensitivity

*From Nature Medicine 10, 355 - 361 (2004)*
Endocrine Disrupting Chemicals (EDCs)

• *Endocrine disrupter* - a compound that mimics or blocks the action of endocrine hormones, either directly or indirectly
  - Often persistent pollutants or dietary components that disturb development, physiology and homeostasis

• Frequently act through nuclear hormone receptors
  - Environmental estrogens
  - Anti-androgens
  - Anti-thyroid

• Recent white paper from the Endocrine Society - Diamanti-Kandarakis, et al, Endocrine Reviews 30 (4): 293-342 (2009)
  - Details scientific support for existence and effects of EDCs
  - Endorsed by American Medical Association
  - Led to H.R. 4190 - Endocrine Disruption Prevention Act of 2009
  - Moves responsibility for research from EPA to NIEHS
Endocrine Disrupting Chemicals (EDCs)

- Are EDC-mediated disturbances in endocrine signaling pathways involved in adipogenesis and obesity
EDCs and the obesogen hypothesis

- **Obesogens** - chemicals that inappropriately stimulate adipogenesis and fat storage, disturb adipose tissue homeostasis, or alter control of appetite/satiety to lead to weight gain and obesity

- Pre- and postnatal exposure to EDCs such as environmental estrogens (ER) increases weight
  - DES, genistein, bisphenol A

- Thiazolidinedione anti-diabetic drugs (PPARγ)
  - Increase fat storage and fat cell number at all ages in humans

- Urinary phthalates correlate with waist diameter and insulin resistance in humans

- Several compounds cause adipocyte differentiation in vitro (PPARγ)
  - Phthalates, BPA, alkylphenols, PFOA, organotins

- Existence of obesogens is plausible
Endocrine disruption by organotins

- Organotins -> imposex in mollusks
- Sex reverses genetically female flounder and zebrafish -> males
- Which hormone receptors might be organotin targets?
- We found that tributyltin (TBT)
  - Binds and activates at ppb (low nM) to two nuclear receptors, RXR and PPARγ critical for adipogenesis
  - TBT induced adipogenesis in cell culture models (nM)
  - Prenatal TBT exposure led to weight gain in mice, in vivo
How does TBT exposure cause weight gain?

- Changes in the hormonal control of appetite and satiety?
- Altered ability of adipocytes to process and store lipids?
- Increased number of adipocytes or pre-adipocytes?
- Mesenchymal stem cells (MSCs) (now called multipotent stromal cells) precursors to many lineages including bone, cartilage, and adipose.
  - MSCs differentiate into adipocytes following rosiglitazone exposure
  - MSCs may (or may not) home to adipose depots after induction
- **Hypothesis**: TBT induces adipogenesis in MSCs
Prenatal TBT exposure increases MSC differentiation into adipocytes

Kirchner et al., 2010 Molec Endocrinol, 24, 526-539
Effects of prenatal TBT on MSC pool

- TBT exposure biases the MSC compartment toward adipocytes
  - 7-15% more pre-adipocytes in TBT-treated than control animals

- Increased expression of adipocyte markers reflects increased number of pre-adipocytes
  - Decreased potential to form osteoblasts

- This suggests that the setpoint for fat cell number has been permanently altered by TBT exposure
  - Implications for obesogen exposure in general?

- TBT is an obesogen that acts through PPARγ to increase fat deposition and body weight while predisposing MSCs to be adipocytes
Conclusions and Implications For Human Health

- Diet and exercise are insufficient to explain obesity epidemic particularly in the very young

- Obesogens inappropriately stimulate adipogenesis and fat storage
  - Prescription drugs
    - Thiazolidinedione anti-diabetic drugs (Actos, Avandia)
    - Atypical antipsychotics, anti-depressants
  - Environmental contaminants
    - organotins, environmental estrogens (BPA, DEHP), PFOS

- Prenatal obesogen exposure reprograms exposed animals to be fat
  - Epigenetic changes alter fate of stem cell compartment -> more preadipocytes and more cells committed to adipocyte lineage

- Obesogens shift paradigm from treatment to prevention during pregnancy, childhood and puberty
  - Reduced exposure to obesogens, optimized nutrition
  - Obesity is intractable once established
Obesogens - Just the Tip of the Iceberg?

- What don’t we know yet?
  - How many obesogens are out there
  - What are the body burdens in populations
  - Molecular targets of action beyond RXR-PPARγ
  - Critical windows of exposure
  - How does prenatal exposure alter adult phenotype?
  - How does diet interact with obesogen exposure?
  - Is the prenatal reprogramming epigenetic?
Human Studies Supporting the Obesogen Hypothesis

- Prenatal & early life exposures to low levels of **PCBs and DDE** are associated with increased weight in boys and girls at puberty (Gladen et al, J. Pediatr., 2000).

- Childhood obesity is associated with **maternal smoking** in pregnancy (Toschke et al, Eur J Pediatr 2002).

- **Soy-based formula** in infancy is a potential risk factor for overweight later in life (Strom et al., JAMA, 2001; Stettler et al., 2005).

- Concentrations of urinary **phthalate** metabolites are associated with increased waist circumference and insulin resistance in adult US males (Stahlhut et al, EHP, 2007).

- Exposure to **hexachlorobenzene** during pregnancy increases the risk of overweight in children aged 6 years (Smink et al, Acta Paediatrica, 2008).

- Intrauterine exposure to environmental pollutants (**POPs**) and body mass during the first 3 years of life (Verhulst et al EHP, 2009).

- Prenatal exposure to **DDE** is associated with rapid weight gain in the first 6 months and elevated BMI later (Mendez et al EHP, 2011).