

Transgenerational Inheritance of Prenatal Obesogen Exposure

Department of Developmental and Cell Biology and Pharmaceutical Sciences, University of California, Irvine, CA, USA

Bruce Blumberg blumberg@uci.edu

Obesity and metabolic syndrome diseases have exploded into an epidemic of global proportions. Consumption of calorie-dense food and diminished physical activity (the calories in-calories out model) are generally accepted to be the causal factors for obesity. But could environmental factors expose preexisting genetic differences or exacerbate the root causes of diet and exercise? The environmental obesogen model proposes that chemical exposure during critical stages in development can influence subsequent adipogenesis, lipid balance and obesity. Obesogens are chemicals that inappropriately stimulate adipogenesis and fat storage. Tributyltin (TBT) is a high-affinity agonistic ligand for both the Retinoid X Receptor (RXR) and Peroxisome Proliferator Activated Receptor gamma (PPAR γ). RXR-PPAR γ signaling is a key component in adipogenesis and the function of adipocytes and activation of this receptor heterodimer can elevate adipose mass in rodents and humans. Thus, inappropriate activation of RXR-PPAR γ can directly alter adipose tissue homeostasis. We previously showed that TBT promoted adipocyte differentiation, modulates adipogenic genes *in vivo*, and increased adiposity in mice after *in utero* exposure. These results are consistent with the environmental obesogen model and suggest that organotin exposure is a previously unappreciated risk factor for the development of obesity and related disorders. Based on the observed effects of TBT on adipogenesis, we hypothesized that organotin exposure during prenatal adipose tissue development might favor the subsequent development of adipocytes. We found that prenatal TBT exposure altered the balance of progenitor types in the multipotent stromal stem cell (MSC) compartment predisposing them to form adipocytes at the expense of bone. Intriguingly, prenatal exposure to low, environmentally relevant doses of TBT delivered in drinking water lead to transgenerational effects on adipose depot weight, adipocyte size and gene expression in MSCs in F1, F2 and F3 animals. We also found that prenatal TBT exposure led to increased hepatic lipid accumulation and up-regulated hepatic expression of genes involved in lipid storage/transport, lipogenesis and lipolysis in all 3 generations. Taken together, these results illustrate how prenatal exposure to xenobiotic compounds can have lasting, potentially permanent effects on the offspring of exposed animals.