Chapter 10
Adipocytes as Target Cells for Endocrine Disruption

Amanda Janesick and Bruce Blumberg

Abstract Throughout the first two decades of human development, growth of adipose tissue primarily results from an increase in adipocyte number (hyperplasia). Once established, the number of fat cells remains relatively constant, and adipose tissue grows larger primarily by filling the resident cells with more fat (hypertrophy). Obese children exhibit an augmented rate of increase in adipocyte number, and correspondingly, obese adults possess more fat cells. Hence, childhood and adolescence appear to be critical periods in establishing the number of fat cells. Endocrine-disrupting chemicals (EDCs) can predispose a child to obesity by influencing all aspects of adipose tissue growth, starting from multipotent stromal cells (MSCs) and ending with mature adipocytes. EDC exposure can increase the number of preadipocytes, enhance the differentiation of preadipocytes into adipocytes, and augment the uptake of fat into existing adipocytes. Unlike genetic mechanisms, which require a mutation event, EDCs have the capacity to quantitatively alter gene expression by modulating cellular-signaling pathways and by introducing epigenetic changes that also alter gene expression. Therefore, EDC exposure could foster a swift change in the metabolic profile of a population, which might provide at least a partial explanation for the rapid rise in obesity. This review focuses on the developmental origins of the adipocyte and its connection to early-onset obesity with the aim of providing a foundation for formulating hypotheses regarding how EDCs can interfere with adipogenesis and contribute to the obesity epidemic.

A. Janesick (✉)
Department of Developmental and Cell Biology, 2011 Biological Sciences 3,
University of California, Irvine, CA, USA
e-mail: ajanesic@uci.edu

B. Blumberg
Department of Developmental and Cell Biology, 2011 Biological Sciences 3,
University of California, Irvine, CA, USA

Department of Pharmaceutical Sciences, University of California, Irvine, CA, USA
e-mail: Blumberg@uci.edu

Keywords Adipocyte • Adipogenesis • Endocrine-disrupting chemical (EDC) • Endocrine disruption • Epigenetic reprogramming • Epigenetics • Multipotent stromal cell (MSC) • Nuclear receptor • Obesity • Obesogen • PPAR gamma • Stem cell • Transgenerational effects

Introduction

On April 20, 2010, a group of retired military leaders reported that 27% of all Americans aged 17–24 were too overweight to join the military [1]. Although current recruitment goals are satisfied, the concern is that this trajectory will continue until only a small proportion of America's youth will be qualified to serve [2]. This is supported by a recent study projecting that by 2030, 86% of Americans will be overweight, contributing to upwards of 900 billion dollars yearly in additional health care costs [3]. Notwithstanding the national security implications, the major concern with childhood obesity is its strong link with and ability to predict adult obesity and metabolic disease [4–7]. Indeed, a recent longitudinal study showed that increased waist diameter and body mass index (BMI) in children and adolescents increased the risk for abdominal obesity, insulin resistance, thrombotic disorder, elevated low-density lipoproteins ("bad" cholesterol), and systemic inflammation, later in life [8, 9]. These are the signatures of metabolic syndrome, and while adults might rise above this outcome, prevention at earlier stages in life would be more effective.

Throughout the first two decades of human development, growth of adipose tissue primarily results from an increase in adipocyte number (hyperplasia) [10, 11]. After this, the number of fat cells remains relatively constant, and adipose tissue grows larger primarily by filling the resident cells with more fat (hypertrophy) [11]. Obese children exhibit an augmented rate of increase in adipocyte number, and correspondingly, obese adults possess more fat cells [10, 11]. Hence, researchers have hypothesized that childhood and adolescent periods are critical in establishing the number of fat cells [12, 13]. The inference is that a child who is overnourished will produce an excess of new fat cells and, in essence, be "stuck" with these cells later in life. In part, this explains why the military leaders suggest school nutrition intervention, and why celebrities like Chef Jamie Oliver champion the eradication of processed foods from school lunch programs [14]. While these are wise choices that will ultimately be beneficial, unfortunately, mounting evidence supports the idea that obesity is established before puberty [15] and even before birth [16]. Genetics is a popular mechanism to explain such a deterministic phenomenon, except that it cannot account for the rapid rise in obesity.

Endocrine-disrupting chemicals (EDCs) have the strong potential to predispose a child to obesity by influencing all aspects of adipose tissue growth, starting from multipotent stromal cells (MSCs) and ending with mature adipocytes [17]. Certain EDCs can create an immutable adipocyte landscape characterized by increased proliferation and differentiation of adipose progenitors, coupled with an inherent

alteration in the MSC compartment that biases stem cells toward the adipose lineage [18]. Unlike genetic mechanisms, which require a mutation event, EDCs have the capacity to quantitatively alter gene expression by modulating cellular-signaling pathways and by introducing epigenetic changes that also alter gene expression. Epigenetic marks in chromatin are programmed during times of developmental plasticity (in the womb or during childhood and adolescence) [19]. Therefore, EDC exposure could foster a swift change in the metabolic profile of a population, which might provide at least a partial explanation for the rapid rise in obesity. This also vindicates the common experience that adipose tissue is often unyielding to shrinkage through improved diet and exercise. Many of the early events in adipogenesis remain unclear, thus, the processes targeted by EDCs may not be fully understood until fundamental mechanisms of adipose development have been resolved. This review focuses on the developmental origins of the adipocyte and its connection to early-onset obesity with the aim of providing a foundation for formulating hypotheses regarding how EDCs can interfere with adipogenesis and contribute to the obesity epidemic.

The Morphology of Adipose Tissue in Early-Onset Obesity

Humans are the fattest of all mammals at birth, typically possessing ~ 15% body fat, of which most is white adipose tissue (WAT) [20]. This is predicted to be the result of high encephalization [21] because our large brains consume an enormous amount of energy. During infancy, body fat composition nearly doubles (to 28%), but then declines during early childhood [22]. After about 8 years of age and throughout adolescence, adipose tissue grows, although the body distribution becomes sexually dimorphic. Males decrease their fat composition as a percentage of total body mass, whereas females increase their fat composition [23]. Under normal circumstances, body fat functions in the proper timing of puberty, again with a sexual dimorphism. A high-percent body fat delays puberty in males, but initiates early menarche in females [24]. Recent research, using 14C labeling, highlighted the childhood and adolescent periods as the main time of adipose hyperplastic growth [11]. In early adulthood, the total number of fat cells stabilizes; the number only increases when existing cells have reached full capacity through hypertrophic growth [11].

While more sophisticated, the 14C-labeling studies actually confirmed long-standing results. Nearly 40 years ago, obesity, particularly early-onset obesity, was linked to hypercellularity of adipose tissue [25–27]. Ten years later, researchers charted the steady increase in adipocytes during the first two decades of life and showed that obese children possessed more fat cells which multiplied at a faster rate than non-obese children [10]. Further studies demonstrated that once established, a person's adipocyte population is resistant to changes in number. For example, obese adolescent girls who were put on a strict diet and advised to engage in physical activity surprisingly showed increased hyperplastic adipocyte growth after 1.5 years, compared to the reference group [28]. Those girls that were most resistant to the

treatment had the greatest increase in adipocyte number. This is supported by the 14C-labeled adipose studies, mentioned above, which also showed that the number of adipocytes remains relatively constant throughout adulthood, is higher in obese individuals, and cannot readily be reduced even after bariatric surgery (although adipocyte volume decreases) [11].

The body's resistance to changes in adipocyte number correlates well with the observation that the body resists major alterations in weight gain or loss. In the 1930s and 1940s, the general belief was that obesity was induced by a lack of will-power [29], perhaps due to some hypothalamic disruption that influenced satiety [30]. However, when obese patients were forced to follow a severe liquid diet, they reached a more normal weight, but this was, by no means, a homeostatic state [31–33]. They exhibited signs of starvation, and a preoccupation with the craving for food, stronger than addiction, an urge akin to an extreme thirst for water or the desire to breathe. In the opposite scenario, lean volunteers from the Vermont State Prison were asked to eat 2–3 times more than usual [34]. The authors of the study stated, "achieving a serious gain in weight cannot be undertaken as a secondary occupation." Although the prisoners gained weight at different rates, they were all able to return to their former weight. Importantly, the prisoners' weight gain was hypertrophic in nature, whereas the starving obese subjects' weight loss was hypotrophic. In each case, the individuals were struggling against their basic biology, their metabolic set point, defined by the number of cells in adipose depots.

Of course, this is not to say that adipocytes are static entities, or that only a fixed number of cells are allocated to each person. Although adipocytes are postmitotic, they do regenerate about once every 10 years [11] through the processes of apoptosis, autophagy, dedifferentiation, or necrosis, and subsequent renewal [35–37]. The adipocyte pool size can fluctuate; a high-fat diet, for example, will encourage hyperplasic growth of subcutaneous fat depots in adult mice [38]. Moreover, when cells have reached their lipid capacity, they will generate paracrine signals that result in the generation of more fat cells in rodents [39–41]. Not all fat tissue is equally capable of hyperplastic growth; in particular, visceral abdominal fat (VAT) does not readily increase its cell number [38, 42]. A very popular hypothesis is that many pathological consequences of obesity are due to excessive adipocyte hypertrophy (as a result of nutrient excess, or an inherent imbalance in fatty acid synthesis and oxidation [43]) coupled with an impaired ability to compensate with adipose tissue expansion [44–48]. The result is adiposopathy [49], which is often characterized by lipotoxicity, where lipid essentially "leaks" into other tissues generating proinflammatory signals and oxidative stress, leading to chronic hyperglycemia and increased circulation of triglycerides [50, 51]. One reason that thiazolidinedione antidiabetic medications are effective is because they protect against this ectopic fat "leakage" by encouraging the birth of new adipocytes in depots other than the VAT, thereby preventing adipocytes from bursting or leaking into the surrounding tissue [52].

Notwithstanding these results, increased adipocyte number, rather than increased size, is the morphology commonly shared among obese individuals who developed the disease early or during adolescence. Furthermore, adipose depot hypercellularity is also the morphology associated with resistance to weight loss. This review

highlights programming events early in life that augment the proliferation and differentiation capacity of adipose precursors resulting in an increased number of fat cells. This is important because the obesity epidemic is now recognized as a crisis trending toward the very young [53]. Hence, there is a strong impetus to understand the mechanisms underlying early fat cell development, and how EDCs can influence the differentiation of preadipocytes to adipocytes and the commitment of stem cells to preadipocytes.

Endocrine Disruption During the Differentiation Phase

In the field of adipose biology, a heightened number of fat cells is simply an end point, and it becomes important to investigate the mechanistic basis. The mature adipocyte is generated from a white adipocyte precursor (often called a "preadipocyte") which is committed to the adipocyte fate and cannot differentiate into any other lineage (like bone, cartilage, muscle, or even brown fat) [54–57]. This precursor is derived from multipotent stromal cells (MSCs) found in almost all fetal and adult tissues [58], but most commonly cultured from adipose tissue or bone marrow. Most evidence supports the theory that MSCs are the progeny of perivascular cells that surround blood vessel walls [59, 60]. In support of this hypothesis, it was recently shown that the white adipose precursor exists within the adipose vascular network [61]. This is not surprising because adipose is a highly vascularized tissue and antiangiogenic agents reduce adipose mass [62, 63]. The differentiation of white adipocyte precursors into mature adipocytes (adipogenesis) is well characterized in the literature. The central regulator in this process is the peroxisome proliferator–activated receptor gamma (PPARγ), which associates with the retinoid X receptor (RXR) and binds DNA targets as a heterodimer [64]. Figure 10.1 depicts the many of the known events in adipocyte differentiation, focusing on their origin from multipotent precursors, the other main pathways that these precursors can differentiate along, commitment to preadipocytes, differentiation, and apoptosis.

PPARγ is first induced at the transcriptional level by CCAAT/enhancer-binding protein (C/EBP) β and δ [65, 66], and then engages in a feed-forward loop with C/EBPα, amplifying the adipogenic signal [67]. However, C/EBPα also induces Sirtuin-1 [68] which curbs adipogenesis via inhibition of PPARγ target genes [69]. The induction of adipogenesis is typically initiated in cell culture by differentiating agents [70] such as insulin, glucocorticoids, and methylisobutylxanthine, which act through the PI3K/AKT (phosphoinositide 3-kinase/AKT), glucocorticoid receptor, and cAMP protein kinase pathways, respectively. This induction cocktail primarily functions to increase the expression level of C/EBPα or PPARγ, not to activate PPARγ via the production of ligand. An exception to this is the insulin-induced transcription factor, sterol regulatory element–binding protein 1c (SREBP1c), which synthesizes fatty acids that can bind PPARγ [71]. Indeed, the fatty acid derivative, 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), is the strongest candidate for an endogenous ligand for PPARγ [72, 73], although 15d-PGJ2 primarily functions
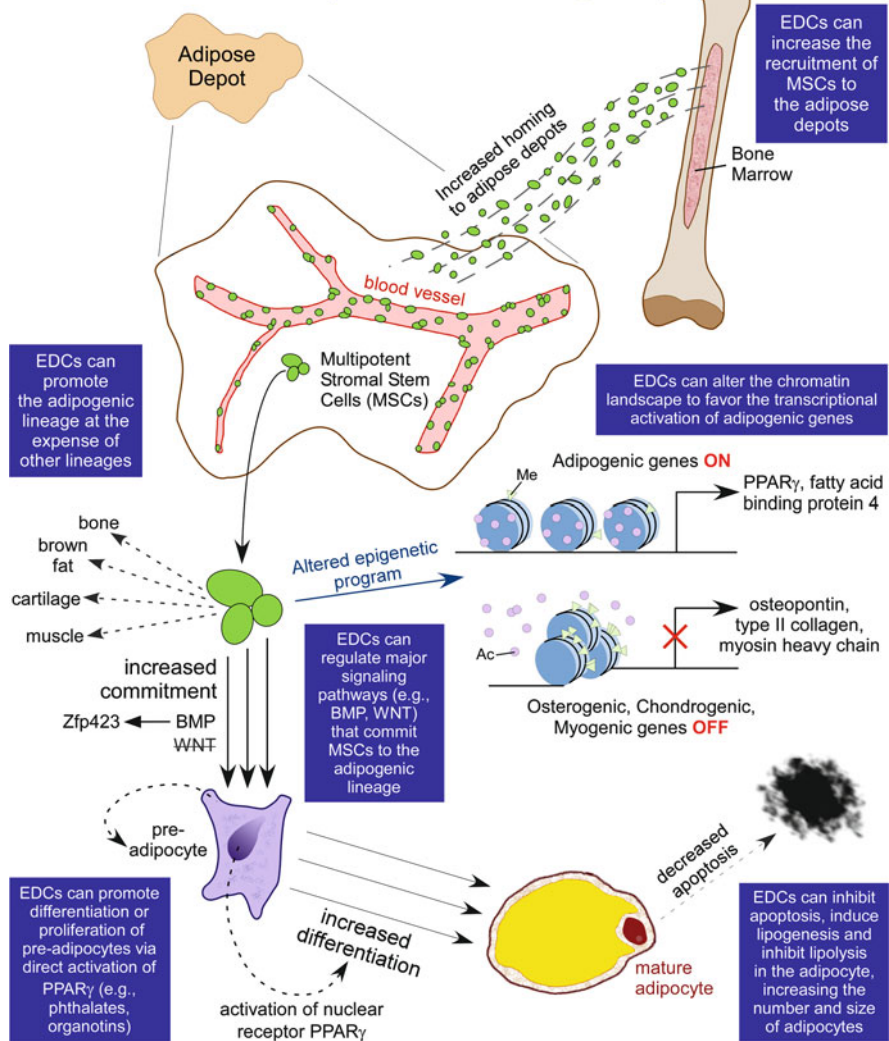
Fig. 10.1 EDCs have the potential to affect multiple aspects of adipocyte development. MSCs reside within the vasculature of adipose depots; however, EDCs could increase homing of circulating MSCs to adipose tissues. EDCs could also alter the epigenetic program of MSCs by turning on the expression of adipogenic genes and turning off osterogenic, chondrogenic, and myogenic genes. These changes, in addition to the possible involvement of EDCs in the modulation of cellular-signaling pathways (BMP, WNT), increase the commitment of MSCs to preadipocytes at the expense of other lineages. EDCs also play a direct role in the differentiation phase by binding PPARγ, promoting the proliferation and differentiation of preadipocytes. Finally, EDCs could exert effects on the mature adipocyte by inhibiting apoptosis, or enhancing the storage of fat, stimulating hypertrophic growth

in angiogenesis [74]. It was recently suggested that PPARγ may function in adipogenesis without requiring the ability to be activated by ligand [75]. However, the ligand-binding domain itself is required. When the ligand-binding domain of PPARγ was mutated, the receptor was unresponsive to known agonists, but the ability of preadipocytes to differentiate into adipocytes was unaffected in cell culture [75]. In contrast, deletion of the activation function 2 region of the ligand-binding domain rendered the receptor unable to support adipogenesis [75].

Several EDCs affect PPARγ activity during adipogenesis. The most well-known synthetic agonists of PPARγ are the thiazolidinedione class of antidiabetic agents including rosiglitazone (ROSI) and pioglitazone (PIO) [76]. In addition to increasing insulin sensitivity, these drugs encourage new fat-cell growth and relieve inflammatory stress from hypertrophic cells, but promote hyperplastic obesity. Environmental chemicals such as certain phthalates [77–79] and organotins [80–82] are agonist ligands for PPARγ. Perfluoroalkyl acids either activate PPARγ weakly [83] or not at all, [84] despite activating PPARα or PPARδ. In cell culture models, phthalates and organotins have the expected effect of promoting preadipocyte differentiation [78, 80]. Importantly, prenatal exposure to tributyltin (TBT) in mice caused substantial storage of triglycerides in newborn tissues that normally have little to no fat at all [80]. The experiments did not distinguish between increased lipid accumulation in existing cells and an increased number of fat cells. However, given the fact that TBT exposure in *Xenopus laevis* tadpoles caused the entire testes to essentially turn into fat, it was concluded that TBT primarily functions to promote new adipocyte development at the expense of other cell types. Further studies (outlined in the next section) were undertaken to understand how TBT biases progenitor cells toward the adipocyte lineage.

To date, TBT is the only EDC known to cause in utero effects on adipocytes via PPARγ. Prenatal exposure to phthalates has not yet been linked to adiposity later in life; although high levels of urinary phthalate metabolites were positively correlated with waist diameter in men [85]. Other EDCs also promote adipogenesis, but do not act through PPARγ. Coplanar PCBs (e.g., PCB-77) bind the aryl hydrocarbon receptor in adipocytes and increase adipogenesis [86]. Bisphenol A (BPA) and BPA-related chemicals including alkylphenols stimulate adipogenesis in cell culture [87]. There are a variety of other nuclear receptors and their cofactors that are activated during adipogenesis [88, 89] including those known to be involved in energy metabolism such as the liver X receptor (LXR), the glucocorticoid receptor (GR) and the thyroid receptor (TR), and those more well known in other non-metabolic pathways such as nuclear receptor–related 1 (NURR-1) and the germ cell nuclear factor (GCNF) [88]. Any of these receptors could potentially be targeted by chemicals. Furthermore, RXR is also upregulated during adipogenesis and is activated by TBT [80, 90]. RXR is an obligate heterodimeric partner for PPARγ, as well as TR, NURR-1, LXR, and PPAR (among many other nuclear receptors). RXR itself can be activated in a subset of these heterodimers.

Despite the fact that many EDCs accumulate in adipose tissue and contribute to local effects, most studies have explored the broader metabolic consequences of EDCs, and then addressed the secondary effects on the adipocyte. For example,

polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) reduce thyroid function [91] possibly by competing for thyroid transport proteins [92]. High levels of maternal PCBs and PBDEs are correlated with reduced total and free T_4 levels in infant cord blood [93]. Thyroid hormone stimulates lipolysis in adipocytes by downregulating phosphodiesterase activity which normally functions to inhibit catecholamine-induced lipolysis [94, 95]. Thyroid hormone also downregulates SREBP1c, resulting in the inhibition of lipogenesis [96]. The inference is that exposure to EDCs like PCBs and PBDEs will reduce thyroid hormone levels and cause a concomitant increase in lipid accumulation in adipocytes. Another large class of EDCs that globally affect energy metabolism is the synthetic estrogens, like diethylstilbestrol (DES) and bisphenol A (BPA) [97]. In adults, estrogens protect against adiposity through exergonic, energy-consuming reactions in glycolysis, fatty acid oxidation, and electron transport [97]. At the level of the adipocyte, estrogen receptor beta (ERβ) blocks the transcriptional activity of PPARγ and, hence, is antiadipogenic but prodiabetogenic [98]. In contrast to their effects in adults, low doses of estrogens given pre- or perinatally strikingly promote obesity in exposed animals [99]. Similarly, nicotine, which promotes weight loss in adults, increases adipose hypertrophy in young rats [100]. The overall conclusion from these studies is that EDCs can impact the differentiation of adipocytes in a variety of ways.

Endocrine Disruption During the Commitment Phase

Recent research has been directed toward understanding the commitment phase of adipocyte development, that is, how MSCs become preadipocytes. Recently, progenitor cells (which later matured into adipocytes) were purified and found to have the following phenotype: lin⁻, CD29⁺, CD34⁺, Sca-1⁺, CD24⁺ [101]. These cells could generate an entire adipose depot in lipodystrophic mice, suggesting that they are bona fide adipocyte precursors [101]. What remains largely unknown is the transcriptional program that turns stem cells into preadipocytes. Bone morphogenic protein (BMP) signaling is not only important in skeletal development but appears to be a vital component in stem cell commitment to the adipocyte lineage [102]. Recently, Zfp423, a downstream target of BMP signaling, was found to be upregulated in fibroblast clones with high adipogenic potential compared with cells having a low adipogenic potential [103]. However, Zfp423 expression remained unchanged during the preadipocyte to adipocyte transition, suggesting that it is involved in the commitment of stem cells to the preadipocyte lineage, but perhaps not in preadipocyte maintenance [103]. In addition to active BMP signaling, repression of noncanonical WNT5a signaling is required for MSCs to evade the osteogenic lineage and proceed toward the adipogenic lineage [104]. This aligns well with the observation that preadipocytes do not differentiate in the presence of WNT signaling [105].

There are very few studies that investigate how EDCs could bias the MSC population toward the adipogenic linage. In cell culture, organophosphates and

4-tertoctylphenol thwarted the bone differentiation capacity of MSCs [106]. When MSCs were cultured from adipose tissue, then treated with TBT or ROSI plus induction cocktail, their proliferation capacity decreased, and up to 60–80% of the cells differentiated into mature fat cells [18]. Cells treated with induction cocktail, but without TBT or ROSI, maintained higher proliferative levels, and only 25–40% of cells became adipocytes [18]. Interestingly, this effect was also seen after in utero exposure. Pregnant dams were treated with a single dose of TBT or ROSI, and the MSCs (cultured from the adipose tissue of embryos) were already predisposed to become fat cells, even without further treatment with TBT or ROSI [18]. In addition, the MSCs harvested from the TBT- or ROSI-exposed pups were preprogrammed to prefer the adipogenic fate because, when induced with bone differentiating cocktail, many cells still differentiated into adipocytes [18]. This suggests that the MSC population in prenatally TBT- or ROSI-treated animals is enriched in adipocyte precursors at the expense of osteoblasts [18]. This mutually exclusivity ability of a subset of MSCs to differentiate into bone or fat is why osteoporosis has been called "obesity of bone" [107, 108]. MSCs cultured from postmenopausal women with low bone density accumulate twofold more lipid and twofold less type I collagen (part of the bone extracellular matrix) compared to women with healthy bones [109]. Not surprisingly, diabetes medications that activate PPARγ increase the risk for bone fractures [110]. The results with TBT suggest that obesogen exposure may have a similar effect on osteoporosis.

The most recent evidence supports the idea that fat cells are regenerated from an existing population of MSCs that are found in the vasculature of adipose depots [61, 101]. However, it is also possible that circulating MSCs derived from bone marrow can be recruited to the depots. The relative contribution of resident and circulating MSCs to the obesogenic phenotype of TBT- or ROSI-treated animals is currently unknown. Most studies of MSC migration have been devoted to how MSCs escape from bone marrow and flood an injury site [111, 112]. MSCs are predicted to move by chemotaxis, losing adherence to their origin, rolling along blood vessels, and moving through the extracellular matrix to the tissue that is injured [113]. By a similar mechanism, these cells could migrate to adipose tissue upon receiving an appropriate signal. This idea was recently tested by transplanting GFP-labeled bone marrow–derived MSCs into irradiated wild-type mice, and determining whether these cells could populate fat pads in response to adipogenic signals [114]. ROSI or a high-fat diet increased migration of circulating bone marrow cells to omental or dorsal intrascapular fat depots [114]. However, this view has been challenged in a subsequent paper, which states that bone marrow–derived circulating progenitor cells fail to differentiate into adipocytes [115]. Whether or not MSCs can be recruited to adipose depots from bone marrow is probably a moot point since it now appears that MSCs are pericytes that are found in close proximity with vasculature. Whether they are solely localized in the bone marrow and adipose vasculature [61, 101] or instead are found throughout the body [59] is currently controversial. More studies will be required to determine where adipogenic MSCs are located, whether or not they migrate to adipose depots in response to dietary stimuli, and what effects EDCs such as TBT and phthalates have on these processes.

Epigenetic Modifications During Puberty

Although ordinary genetic variability can account for why some people have the propensity to become obese, the rapid increase in obesity argues against a genetic explanation. Epigenetic phenomena occur much faster than gradual genetic mutation and can easily become established in a population within a single generation [116]. For this reason, epigenetics is a more likely explanation for the "epidemic" of obesity. Moreover, epigenetics can also underlie the rapid metabolic adaptations that occur in the womb under dietary stress, and perhaps during other developmental time windows, such as adolescence. While EDCs such as TBT can act on adipose tissue directly (e.g., by binding to PPARγ and inducing adipocyte differentiation), they can also target adipose development via more subtle, epigenetic modifications. EDC exposure has been linked with alterations in the expression of proteins that remodel the chromatin landscape, such as DNA methyltransferases, histone acetyltransferases, deacetylases, and methyltransferases. For example, in the uteri of animals that were prenatally exposed to DES, there was a significant increase in the mRNA expression of DNA methyltransferase 1 (Dnmt1) and DNA methyltransferase 3b (Dnmt3b) [117]. In another example, exposure to the commonly used fungicide vinclozolin caused a decrease in the expression of Dnmt1, Dnmt3a, Dnmt3L, and euchromatic histone methyltransferase (Ehmt1) in the testes of male rats, and some of these genes remained inhibited in subsequent generations [118].

Since EDCs typically have targeted effects on a particular metabolic pathway, the question of specificity arises. It was shown that Dnmt1 and Dnmt3 can be recruited to individual genes simply by being escorted by transcription factors to specific sequences of DNA, suggesting that the specificity of the EDC effect is conferred by the active transcriptional programs in individual cells [119, 120]. Of course, identification of bona fide DNA sequences (often CpG islands) modulated by EDCs is a challenge and requires a genomic approach. Over 6,000 genes have been predicted to affect body mass, and there are ten times more genes that foster an increase in weight, rather than a decrease [121]. It is likely that epigenetic changes related to adipogenesis and obesity originate within the stem cell compartment. The reason that diet and exercise primarily alter adipocyte volume rather than adipocyte number is because the stem cells are already biased, through changes in gene regulation, to replenish the adipocyte pool to its "set point," if for any reason the number of adipocytes declines. In support of this model, MSCs from mice exposed to TBT in utero exhibited alterations in the methylation status of the CpG islands of adipogenic genes such as AP2 and PPARγ which led to an increase in the number of preadipocytes at birth and an increased propensity to differentiate into adipocytes upon stimulation [18].

Even more profound is the possibility that epigenetic changes caused by environmental exposures are accumulated or inherited across generations. Vinclozolin, for example, is linked to infertility throughout multiple generations, [122] due to a "memory" maintained within the male germ cells [123]. While there are currently no data regarding transgenerational effects of obesogens, it is reasonable to hypothesize

that obesogenic compounds such as TBT, BPA, or phthalates could also influence the propensity to be obese for some generations after the initial exposure. An example in humans serves to illustrate this point. In the Overkalix region of Sweden, it was demonstrated that food availability during the prepubescent period affected the longevity and mortality from cardiovascular disease of a boy's grandchildren. A single winter of overeating could lead to a 6-year decrease in longevity of a boy's grandsons, but not granddaughters [124]. While this is a nutritional study, it is quite possible that chemical exposure during development could have similar transgenerational effects. The human prepubescent period is especially susceptible to epigenetic changes because the testes or ovaries are developing, and the primordial germ cells incorporate sex-specific imprinting patterns in mice [125]. One hypothesis proposed to explain the Overkalix phenomenon is that stress caused by improper nutrition affects downstream proteins involved in imprinting [126]. One such protein candidate is BORIS (Brother of the Regulator of Imprinted Sites) which is expressed in the male testes only in germ cells undergoing genome remethylation [127]. During the prepubescent period, an exogenous chemical could regulate BORIS and permanently impact the methylation status of DNA. Hence, while it is debatable whether adolescence is the most critical period in establishing obesity, it is likely to be a period when epigenetic changes can be "locked in" for the future.

Conclusion

A somewhat vestigial function of the adipocyte, especially in Western societies, is its incredibly efficient storage capacity for fat. Hence, a resounding presumption is that unhealthy eating and a convenience food-driven society are enabling agents that contribute to self-induced corpulence. However, babies, children, and adolescents seem destined, almost programmed, to keep their "baby fat" throughout life. We have argued that the morphology of adipose tissue associated with early-onset obesity provides a basis for why weight loss in obese people (the state of being "reduced obese") is not often a homeostatic state of normalcy and weight gain is observed in more than 90% of cases. We argued that EDCs could exacerbate this problem by increasing the differentiation capacity of preadipocytes, or biasing the MSC pool toward the adipocyte lineage. Moreover, we discussed how EDCs have the potential to affect epigenetic reprogramming events that might cause irreversible modifications that create transgenerational inheritance of obesity.

The concept of early disruption in adipocyte development explains why each person seems to possess a metabolic set point, which is regulated like a thermostat. The thermostat will resist change in temperature, no matter if a window is opened or a hot oven is turned on. If the set point is altered, the new temperature will be maintained. Early nutrition and chemical exposure could alter an individual's set point, making the fight against weight gain that much more difficult. Obesity is difficult to reverse once established; therefore, it makes sense to shift the focus toward preventative measures. On May 11, 2010, First Lady Michelle Obama launched a

campaign called Let's Move! As a result of strong communication between science and politics, Mrs. Obama drew attention to EDCs, calling for increased research in this area, reformulation of plastics, and screening for chemicals that are obesogenic [128]. With national attention to this problem, the hope is that the contribution of EDCs to the obesity epidemic will finally be recognized so that appropriate action can be taken to reduce exposure at critical periods during life.

References

1. Christeson W, Taggart AD, Messner-Zidell S. Too fat to fight. Washington DC: Mission: Readiness; 2010.
2. Kiernan M, Eismeier T. 9 million young adults are too overweight to join the military. New report shows: Mission: Readiness; 2010.
3. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity. 2008;16(10):2323–30.
4. Guo SS, Roche AF, Chumlea WC, Gardner JD, Siervogel RM. The predictive value of childhood body mass index values for overweight at age 35 y. Am J Clin Nutr. 1994;59(4):810–9.
5. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med. 1992;327(19):1350–5.
6. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997;337(13):869–73.
7. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. Am J Clin Nutr. 2002;76(3):653–8.
8. Grundy SM, Brewer Jr HB, Cleeman JI, Smith Jr SC, Lenfant C. Definition of metabolic syndrome: report of the national heart, lung, and blood institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004;109(3):433–8.
9. Sun SS, Liang R, Huang TT, et al. Childhood obesity predicts adult metabolic syndrome: the Fels longitudinal study. J Pediatr. 2008;152(2):191–200.
10. Knittle JL, Timmers K, Ginsberg-Fellner F, Brown RE, Katz DP. The growth of adipose tissue in children and adolescents. Cross-sectional and longitudinal studies of adipose cell number and size. J Clin Invest. 1979;63(2):239–46.
11. Spalding KL, Arner E, Westermark PO, et al. Dynamics of fat cell turnover in humans. Nature. 2008;453(7196):783–7.
12. Dietz WH. Critical periods in childhood for the development of obesity. Am J Clin Nutr. 1994;59(5):955–9.
13. Dietz WH. Periods of risk in childhood for the development of adult obesity–what do we need to learn? J Nutr. 1997;127(9):1884S–6S.
14. Wishnow J. Jamie Oliver's TED prize wish: teach every child about food. Long Beach. 2010.
15. Wardle J, Brodersen NH, Cole TJ, Jarvis MJ, Boniface DR. Development of adiposity in adolescence: five year longitudinal study of an ethnically and socioeconomically diverse sample of young people in Britain. BMJ. 2006;332(7550):1130–5.

16. Gluckman PD, Hanson MA, Beedle AS, Raubenheimer D. Fetal and neonatal pathways to obesity. Front Horm Res. 2008;36:61–72.
17. Janesick A, Blumberg B. The role of environmental obesogens in the obesity epidemic. In: Lustig RH, editor. Obesity before birth, vol. 30. New York: Springer; 2011. p. 383–399.
18. Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. Mol Endocrinol. 2010;24(3):526–39.
19. Hanson MA, Gluckman PD. Developmental origins of health and disease: new insights. Basic Clin Pharmacol Toxicol. 2008;102(2):90–3.
20. Kuzawa CW. Adipose tissue in human infancy and childhood: an evolutionary perspective. Am J Phys Anthropol. 1998;Suppl 27:177–209. Volume 107, Issue Supplement 27 (Supplement: Yearbook of Physical Anthropology).
21. Foley RA, Lee PC. Ecology and energetics of encephalization in hominid evolution. Philos Trans R Soc Lond B Biol Sci. 1991;334(1270):223–31; discussion 232.
22. Hager A, Sjostrm L, Arvidsson B, Bjorntorp P, Smith U. Body fat and adipose tissue cellularity in infants: a longitudinal study. Metabolism. 1977;26(6):607–14.
23. Rogol AD, Roemmich JN, Clark PA. Growth at puberty. J Adolesc Health. 2002;31(6 Suppl):192–200.
24. Lee JM, Kaciroti N, Appugliese D, Corwyn RF, Bradley RH, Lumeng JC. Body mass index and timing of pubertal initiation in boys. Arch Pediatr Adolesc Med. 2010;164(2):139–44.
25. Hirsch J, Knittle JL. Cellularity of obese and nonobese human adipose tissue. Fed Proc. 1970;29(4):1516–21.
26. Knittle JL. Obesity in childhood: a problem in adipose tissue cellular development. J Pediatr. 1972;81(6):1048–59.
27. Salans LB, Cushman SW, Weismann RE. Studies of human adipose tissue. Adipose cell size and number in nonobese and obese patients. J Clin Invest. 1973;52(4):929–41.
28. Hager A, Sjorstrom L, Arvidsson B, Bjorntorp P, Smith U. Adipose tissue cellularity in obese school girls before and after dietary treatment. Am J Clin Nutr. 1978;31(1):68–75.
29. Newburgh LH, Johnston MW. The nature of obesity. J Clin Invest. 1930;8(2):197–213.
30. Hetherington AW, Ranson SW. The spontaneous activity and food intake of rats with hypothalamic lesions. Am J Physiol. 1942;136(4):609–17.
31. Glucksman ML, Hirsch J. The response of obese patients to weight reduction I. A clinical evaluation of behavior. Psychosom Med. 1968;30(1):1–11.
32. Glucksman ML, Hirsch J. The response of obese patients to weight reduction III. The perception of body size. Psychosom Med. 1969;31(1):1–7.
33. Glucksman ML, Hirsch J, McCully RS, Barron BA, Knittle JL. The response of obese patients to weight reduction II. A quantitative evaluation of behavior. Psychosom Med. 1968;30(4):359–73.
34. Sims EA, Horton ES. Endocrine and metabolic adaptation to obesity and starvation. Am J Clin Nutr. 1968;21(12):1455–70.
35. Gesta S, Tseng YH, Kahn CR. Developmental origin of fat: tracking obesity to its source. Cell. 2007;131(2):242–56.
36. Prins JB, O'Rahilly S. Regulation of adipose cell number in man. Clin Sci (Lond). 1997;92(1):3–11.
37. Singh R, Xiang Y, Wang Y, et al. Autophagy regulates adipose mass and differentiation in mice. J Clin Invest. 2009;119(11):3329–39.
38. Joe AW, Yi L, Even Y, Vogl AW, Rossi FM. Depot-specific differences in adipogenic progenitor abundance and proliferative response to high-fat diet. Stem Cells. 2009;27(10):2563–70.
39. Lau DC, Shillabeer G, Wong KL, Tough SC, Russell JC. Influence of paracrine factors on preadipocyte replication and differentiation. Int J Obes. 1990;14(Suppl 3):193–201.
40. Marques BG, Hausman DB, Martin RJ. Association of fat cell size and paracrine growth factors in development of hyperplastic obesity. Am J Physiol. 1998;275(6 Pt 2):R1898–908.
41. Shillabeer G, Forden JM, Lau DC. Induction of preadipocyte differentiation by mature fat cells in the rat. J Clin Invest. 1989;84(2):381–7.

42. Adams M, Montague CT, Prins JB, et al. Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. J Clin Invest. 1997;100(12):3149–53.

43. Lelliott C, Vidal-Puig AJ. Lipotoxicity, an imbalance between lipogenesis de novo and fatty acid oxidation. Int J Obes Relat Metab Disord. 2004;28(Suppl 4):S22–8.

44. Heilbronn L, Smith SR, Ravussin E. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. Int J Obes Relat Metab Disord. 2004;28(Suppl 4):S12–21.

45. Kim JY, van de Wall E, Laplante M, et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest. 2007;117(9):2621–37.

46. Virtue S, Vidal-Puig A. It's not how fat you are, it's what you do with it that counts. PLoS Biol. 2008;6(9):e237.

47. Gustafson B, Gogg S, Hedjazifar S, Jenndahl L, Hammarstedt A, Smith U. Inflammation and impaired adipogenesis in hypertrophic obesity in man. Am J Physiol Endocrinol Metab. 2009 American Journal of Physiology, vol. 297, no. 5, pp. E999–E1003.

48. Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. Diabetologia. 2000;43(12):1498–506.

49. Bays HE, Gonzalez-Campoy JM, Henry RR, et al. Is adiposopathy (sick fat) an endocrine disease? Int J Clin Pract. 2008;62(10):1474–83.

50. de Ferranti S, Mozaffarian D. The perfect storm: obesity, adipocyte dysfunction, and metabolic consequences. Clin Chem. 2008;54(6):945–55.

51. Gregor MG, Hotamisligil GS. Adipocyte stress: the endoplasmic reticulum and metabolic disease. J Lipid Res. 2007;48:1905–14.

52. Medina-Gomez G, Gray SL, Yetukuri L, et al. PPAR gamma 2 prevents lipotoxicity by controlling adipose tissue expandability and peripheral lipid metabolism. PLoS Genet. 2007;3(4):e64.

53. Lee JM, Pilli S, Gebremariam A, et al. Getting heavier, younger: trajectories of obesity over the life course. Int J Obes (Lond). 2010;34(4):614–23.

54. Park KW, Halperin DS, Tontonoz P. Before they were fat: adipocyte progenitors. Cell Metab. 2008;8(6):454–7.

55. Seale P, Bjork B, Yang W, et al. PRDM16 controls a brown fat/skeletal muscle switch. Nature. 2008;454(7207):961–7.

56. Timmons JA, Wennmalm K, Larsson O, et al. Myogenic gene expression signature establishes that brown and white adipocytes originate from distinct cell lineages. Proc Natl Acad Sci USA. 2007;104(11):4401–6.

57. Cornelius P, MacDougald OA, Lane MD. Regulation of adipocyte development. Annu Rev Nutr. 1994;14:99–129.

58. da Silva Meirelles L, Chagastelles PC, Nardi NB. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J Cell Sci. 2006;119(Pt 11):2204–13.

59. Crisan M, Yap S, Casteilla L, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell. 2008;3(3):301–13.

60. da Silva ML, Caplan AI, Nardi NB. In search of the in vivo identity of mesenchymal stem cells. Stem Cells. 2008;26(9):2287–99.

61. Tang W, Zeve D, Suh JM, et al. White fat progenitor cells reside in the adipose vasculature. Science. 2008;322(5901):583–6.

62. Rupnick MA, Panigrahy D, Zhang CY, et al. Adipose tissue mass can be regulated through the vasculature. Proc Natl Acad Sci USA. 2002;99(16):10730–5.

63. Kahn CR. Medicine. Can we nip obesity in its vascular bud? Science. 2008;322(5901):542–3.

64. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. Cell. 1994;79(7):1147–56.

65. Wu Z, Bucher NL, Farmer SR. Induction of peroxisome proliferator-activated receptor gamma during the conversion of 3 T3 fibroblasts into adipocytes is mediated by C/EBPbeta, C/EBPdelta, and glucocorticoids. Mol Cell Biol. 1996;16(8):4128–36.

66. Shao D, Lazar MA. Peroxisome proliferator activated receptor gamma, CCAAT/enhancer-binding protein alpha, and cell cycle status regulate the commitment to adipocyte differentiation. J Biol Chem. 1997;272(34):21473–8.

67. Rosen ED, Sarraf P, Troy AE, et al. PPAR gamma is required for the differentiation of adipose tissue in vivo and in vitro. Mol Cell. 1999;4(4):611–7.

68. Jin Q, Zhang F, Yan T, et al. C/EBPalpha regulates SIRT1 expression during adipogenesis. Cell Res. 2010;20(4):470–9.

69. Picard F, Kurtev M, Chung N, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature. 2004;429(6993):771–6.

70. Student AK, Hsu RY, Lane MD. Induction of fatty acid synthetase synthesis in differentiating 3 T3-L1 preadipocytes. J Biol Chem. 1980;255(10):4745–50.

71. Kim JB, Wright HM, Wright M, Spiegelman BM. ADD1/SREBP1 activates PPARgamma through the production of endogenous ligand. Proc Natl Acad Sci USA. 1998;95(8):4333–7.

72. Kliewer SA, Lenhard JM, Willson TM, Patel I, Morris DC, Lehmann JM. A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation. Cell. 1995;83(5):813–9.

73. Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. Cell. 1995;83(5):803–12.

74. Kim EH, Surh YJ. The role of 15-deoxy-delta(12,14)-prostaglandin J(2), an endogenous ligand of peroxisome proliferator-activated receptor gamma, in tumor angiogenesis. Biochem Pharmacol. 2008;76(11):1544–53.

75. Walkey CJ, Spiegelman BM. A functional peroxisome proliferator-activated receptor-gamma ligand-binding domain is not required for adipogenesis. J Biol Chem. 2008;283(36):24290–4.

76. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J Biol Chem. 1995;270(22):12953–6.

77. Bility MT, Thompson JT, McKee RH, et al. Activation of mouse and human peroxisome proliferator-activated receptors (PPARs) by phthalate monoesters. Toxicol Sci. 2004;82(1):170–82.

78. Hurst CH, Waxman DJ. Activation of PPARalpha and PPARgamma by environmental phthalate monoesters. Toxicol Sci. 2003;74(2):297–308.

79. Feige JN, Gelman L, Rossi D, et al. The endocrine disruptor monoethyl-hexyl-phthalate is a selective peroxisome proliferator-activated receptor gamma modulator that promotes adipogenesis. J Biol Chem. 2007;282(26):19152–66.

80. Grun F, Watanabe H, Zamanian Z, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. Mol Endocrinol. 2006;20(9):2141–55.

81. Kanayama T, Kobayashi N, Mamiya S, Nakanishi T, Nishikawa J. Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor gamma/retinoid X receptor pathway. Mol Pharmacol. 2005;67(3):766–74.

82. Hiromori Y, Nishikawa J, Yoshida I, Nagase H, Nakanishi T. Structure-dependent activation of peroxisome proliferator-activated receptor (PPAR) gamma by organotin compounds. Chem Biol Interact. 2009;180(2):238–44.

83. Vanden Heuvel JP, Thompson JT, Frame SR, Gillies PJ. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-alpha, -beta, and -gamma, liver X receptor-beta, and retinoid X receptor-alpha. Toxicol Sci. 2006;92(2):476–89.

84. Takacs ML, Abbott BD. Activation of mouse and human peroxisome proliferator-activated receptors (alpha, beta/delta, gamma) by perfluorooctanoic acid and perfluorooctane sulfonate. Toxicol Sci. 2007;95(1):108–17.

85. Stahlhut RW, van Wijngaarden E, Dye TD, Cook S, Swan SH. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ Health Perspect. 2007;115(6):876–82.

86. Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ Health Perspect. 2008;116(6):761–8.

87. Masuno H, Iwanami J, Kidani T, Sakayama K, Honda K. Bisphenol a accelerates terminal differentiation of 3 T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. Toxicol Sci. 2005;84(2):319–27.

88. Fu M, Sun T, Bookout AL, et al. A nuclear receptor atlas: 3 T3-L1 adipogenesis. Mol Endocrinol. 2005;19(10):2437–50.

89. Rosen ED, MacDougald OA. Adipocyte differentiation from the inside out. Nat Rev Mol Cell Biol. 2006;7(12):885–96.

90. le Maire A, Grimaldi M, Roecklin D, et al. Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors. EMBO Rep. 2009;10(4):367–73.

91. Hallgren S, Sinjari T, Hakansson H, Darnerud PO. Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. Arch Toxicol. 2001;75(4):200–8.

92. Cheek AO, Kow K, Chen J, McLachlan JA. Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. Environ Health Perspect. 1999;107(4):273–8.

93. Herbstman JB, Sjodin A, Apelberg BJ, et al. Birth delivery mode modifies the associations between prenatal polychlorinated biphenyl (PCB) and polybrominated diphenyl ether (PBDE) and neonatal thyroid hormone levels. Environ Health Perspect. 2008;116(10):1376–82.

94. Smith CJ, Vasta V, Degerman E, Belfrage P, Manganiello VC. Hormone-sensitive cyclic GMP-inhibited cyclic AMP phosphodiesterase in rat adipocytes. Regulation of insulin- and cAMP-dependent activation by phosphorylation. J Biol Chem. 1991;266(20):13385–90.

95. Van Inwegen RG, Robison GA, Thompson WJ. Cyclic nucleotide phosphodiesterases and thyroid hormones. J Biol Chem. 1975;250(7):2452–6.

96. Viguerie N, Millet L, Avizou S, Vidal H, Larrouy D, Langin D. Regulation of human adipocyte gene expression by thyroid hormone. J Clin Endocrinol Metab. 2002;87(2):630–4.

97. Chen JQ, Brown TR, Russo J. Regulation of energy metabolism pathways by estrogens and estrogenic chemicals and potential implications in obesity associated with increased exposure to endocrine disruptors. Biochim Biophys Acta. 2009;1793(7):1128–43.

98. Foryst-Ludwig A, Clemenz M, Hohmann S, et al. Metabolic actions of estrogen receptor beta (ERbeta) are mediated by a negative cross-talk with PPARgamma. PLoS Genet. 2008;4(6): e1000108.

99. Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. Mol Cell Endocrinol. 2009;304(1–2):84–9.

100. Somm E, Schwitzgebel VM, Vauthay DM, et al. Prenatal nicotine exposure alters early pancreatic islet and adipose tissue development with consequences on the control of body weight and glucose metabolism later in life. Endocrinology. 2008;149(12):6289–99.

101. Rodeheffer MS, Birsoy K, Friedman JM. Identification of white adipocyte progenitor cells in vivo. Cell. 2008;135(2):240–9.

102. Tang QQ, Otto TC, Lane MD. Commitment of C3H10T1/2 pluripotent stem cells to the adipocyte lineage. Proc Natl Acad Sci USA. 2004;101(26):9607–11.

103. Gupta RK, Arany Z, Seale P, et al. Transcriptional control of preadipocyte determination by Zfp423. Nature. 2010;464(7288):619–23.

104. Bilkovski R, Schulte DM, Oberhauser F, et al. Role of WNT-5a in the determination of human mesenchymal stem cells into preadipocytes. J Biol Chem. 2010;285(9):6170–8.

105. Ross SE, Hemati N, Longo KA, et al. Inhibition of adipogenesis by Wnt signaling. Science. 2000;289(5481):950–3.

106. Hoogduijn MJ, Rakonczay Z, Genever PG. The effects of anticholinergic insecticides on human mesenchymal stem cells. Toxicol Sci. 2006;94(2):342–50.

107. Rosen CJ, Bouxsein ML. Mechanisms of disease: is osteoporosis the obesity of bone? Nat Clin Pract Rheumatol. 2006;2(1):35–43.

108. Verma S, Rajaratnam JH, Denton J, Hoyland JA, Byers RJ. Adipocytic proportion of bone marrow is inversely related to bone formation in osteoporosis. J Clin Pathol. 2002;55(9): 693–8.
109. Rodriguez JP, Montecinos L, Rios S, Reyes P, Martinez J. Mesenchymal stem cells from osteoporotic patients produce a type I collagen-deficient extracellular matrix favoring adipogenic differentiation. J Cell Biochem. 2000;79(4):557–65.
110. Habib ZA, Havstad SL, Wells K, Divine G, Pladevall M, Williams LK. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010;95(2):592–600.
111. Hofstetter CP, Schwarz EJ, Hess D, et al. Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. Proc Natl Acad Sci USA. 2002;99(4):2199–204.
112. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. Nature. 2001;410(6829):701–5.
113. Liu ZJ, Zhuge Y, Velazquez OC. Trafficking and differentiation of mesenchymal stem cells. J Cell Biochem. 2009;106(6):984–91.
114. Crossno Jr JT, Majka SM, Grazia T, Gill RG, Klemm DJ. Rosiglitazone promotes development of a novel adipocyte population from bone marrow-derived circulating progenitor cells. J Clin Invest. 2006;116(12):3220–8.
115. Koh YJ, Kang S, Lee HJ, et al. Bone marrow-derived circulating progenitor cells fail to transdifferentiate into adipocytes in adult adipose tissues in mice. J Clin Invest. 2007;117(12): 3684–95.
116. Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. Trends Ecol Evol. 2005;20(10):527–33.
117. Bromer JG, Wu J, Zhou Y, Taylor HS. Hypermethylation of homeobox A10 by in utero diethylstilbestrol exposure: an epigenetic mechanism for altered developmental programming. Endocrinology. 2009;150(7):3376–82.
118. Anway MD, Rekow SS, Skinner MK. Transgenerational epigenetic programming of the embryonic testis transcriptome. Genomics. 2008;91(1):30–40.
119. Robertson KD, Ait-Si-Ali S, Yokochi T, Wade PA, Jones PL, Wolffe AP. DNMT1 forms a complex with Rb, E2F1 and HDAC1 and represses transcription from E2F-responsive promoters. Nat Genet. 2000;25(3):338–42.
120. Burgers WA, Fuks F, Kouzarides T. DNA methyltransferases get connected to chromatin. Trends Genet. 2002;18(6):275–7.
121. Reed DR, Lawler MP, Tordoff MG. Reduced body weight is a common effect of gene knockout in mice. BMC Genet. 2008;9:4.
122. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005;308(5727):1466–9.
123. Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors. Endocrinology. 2006;147(6 Suppl):S43–9.
124. Kaati G, Bygren LO, Pembrey M, Sjostrom M. Transgenerational response to nutrition, early life circumstances and longevity. Eur J Hum Genet. 2007;15(7):784–90.
125. Hajkova P, Erhardt S, Lane N, et al. Epigenetic reprogramming in mouse primordial germ cells. Mech Dev. 2002;117(1–2):15–23.
126. Pembrey ME. Time to take epigenetic inheritance seriously. Eur J Hum Genet. 2002;10(11): 669–71.
127. Loukinov DI, Pugacheva E, Vatolin S, et al. BORIS, a novel male germ-line-specific protein associated with epigenetic reprogramming events, shares the same 11-zinc-finger domain with CTCF, the insulator protein involved in reading imprinting marks in the soma. Proc Natl Acad Sci USA. 2002;99(10):6806–11.
128. Obama M, Barnes M. Solving the problem of childhood obesity within a generation. Washington DC; 2010 http://www.letsmove.gov/sites/letsmove.gov/files/TaskForce_on_Childhood_Obesity_May2010_FullReport.pdf.