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Review

Bone and fat: A relationship of different shades

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ABSTRACT

Environmental and behavioral changes which occurred over the last century led simultaneously to a remarkable increase in human lifespan and to the development of health problems associated with functional impairment of organs either regulating or dependent on balanced energy metabolism. Diseases such as diabetes, obesity and osteoporosis are prevalent in our society and pose major challenges with respect to the overall health and economy. Therefore, better understanding of regulatory axes between bone and fat may provide the basis for development of strategies which will treat these diseases simultaneously and improve health and life quality of elderly.

Introduction

In recent years we are witnessing a remarkable explosion of research illuminating a relationship between bone and energy metabolism. Although central and sympathetic nervous systems as well as gastrointestinal and pancreatic axes play an essential role in systemic regulation of energy metabolism, the role of fat tissue in thia regulation is the most prominent due to its fundamental function in storing and dissipating energy. In the last two decades significant progress has been made in understanding fat tissue origin, its diverse functions, and pathophysiological consequences of its impairment. These advances lead to the finding that fat tissue metabolism is linked to bone homeostasis.

Obesity, diabetes and osteoporosis are major public health concerns. Current estimates indicate that the US population consists of 25% obese, 30% diabetic and prediabetic, and 50% of elderly are osteoporotic individuals. Mechanistically these pathologies share several features including common regulators of bone homeostasis and energy metabolism. Peroxisome proliferator-activated receptor gamma (PPARγ[1]) plays a prominent role in these processes since it controls both energy turnover in adipose tissue and bone turnover [1,2]. In the light of evidence suggesting that bone is an organ integrated with energy metabolism system in respect to energy storage and regulation of energy balance, PPARγ nuclear receptor may be considered as a factor facilitating this integration.

This review is summarizing clinical and translational research findings on the association between fat metabolic status and bone mass. It also attempts to bring a perspective on the role of bone marrow fat in regulation of local milieu supporting bone homeostasis.

Color shades of fat reflect its metabolic function

Fat tissue stores and releases energy under conditions of feeding and fasting, and regulates energy balance in peripheral tissues through its endocrine activities. Adipocytes accumulate energy in the form of lipids and burn it in the process of fatty acid β-oxidation. In addition, fat cells produce adipokines, among them leptin and adiponectin, which in endocrine manner regulate calorie intake and insulin sensitivity. The multiplex of fat functions is sequestered throughout different fat depots. A role of mitochondria-sparse white adipose tissue (WAT), which is represented by visceral and subcutaneous fat, is to store energy in the form of lipids and endocrinal regulation of insulin sensitivity and glucose metabolism in liver and muscle. In contrast, a role of mitochondria-enriched brown adipose tissue (BAT), which is distributed in

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[1] *Abbreviations used:* PPARγ, peroxisome proliferator-activated receptor gamma; WAT, white adipose tissue; BAT, brown adipose tissue; UCP1, uncoupling protein 1; Dio2, deiodinase 2; T4, thyroxine; T3, triiodothyronine; BMAT, bone marrow adipose tissue; MSCs, mesenchymal stem cells; FoxC2, forkhead box C2.

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adult humans as discrete deposits located in the neck, supraclavicular, paravertebral, and suprarenal regions [3], is to dissipate energy to support adaptive thermogenesis [4]. This is mediated by uncoupling protein 1 (UCP1), which stimulates proton leak from the mitochondrial membrane to uncouple respiration from ATP synthesis to produce heat. BAT thermogenic activity is controlled by the central nervous system *via* catecholamines and β-adrenergic signaling, and deiodinase 2 (Dio2)-mediated thyroid hormone conversion from thyroxine (T4) to triiodothyronine (T3). Along with its role in adaptive thermogenesis, BAT also functions in protecting against obesity, insulin resistance and diabetes [5–8]. Genetic ablation of BAT in rodents results in diet-induced obesity, diabetes and hyperlipidemia [9]. In humans, BAT activity correlates negatively with impairment in energy metabolism seen with aging, diabetes and obesity [10]. In conclusion, BAT plays an important role in systemic regulation of glucose metabolism.

It has been recognized that BAT may come from two different origins. The classical preformed BAT originates from Myf5-positive dermomyotomal progenitors, which also give rise to skin and muscle, and functions in non-shivering thermogenesis [11]. In contrast, the Myf5-negative progenitors can differentiate to white adipocytes with function in energy storage or to BAT-like or "beige" adipocytes, which have characteristics of both brown and white fat cells [12]. The BAT-like phenotype can be induced in WAT-type adipocytes by several mechanisms comprising either cold exposure, endocrine action of FGF21 [13], irisin [14], or transcriptional regulators including FoxC2 [15], PRDM16 [16], and PPARγ that is activated with specific agonists [17] which cause SirT1-mediated deacetylation of PPARγ protein [18]. Beige fat possesses strong anti-obesity and anti-diabetic activity. An overexpression of BAT-specific transcription factors, either FoxC2 or PRDM16 in WAT adipocytes, protects mice from diet-induced obesity and metabolic dysfunction [16]. On the other hand, an ablation of beige adipocytes by adipocyte-specific deletion of the transcriptional regulator PRDM16 leads to animals prone to development of diet-induced obesity and severe insulin resistance [19].

Since the beige phenotype can be induced in differentiated WAT depots, it suggests a local function of beige adipocytes within the WAT, perhaps associated with energy dissipation and thermogenesis [16,20,21]. Although beige adipocytes have been identified in human subcutaneous fat, an extent of their contribution to the regulation of energy metabolism is still debatable [12,22]. Improvement in detection of beige adipocytes using specific biomarkers will allow for quantitative assessment of their occurrence and correlation with conditions of altered energy metabolism. Up to date, several gene biomarkers have been suggested based on their relative expression in all three types of adipocytes. Thus, gene transcripts for UCP1 and Zic1 seem to be specific for brown, Tbx1 and TMEM26 for beige, and LEP for white adipocytes [12,22–25].

Bone marrow adipose tissue (BMAT) accumulates in long bones and vertebrae, and fills almost entire marrow cavity by the 3rd decade of human life [26]. In C57BL/6 mice, marrow fat is not detectable up to approximately 4 mo of age, after which it accumulates in long bones progressively with age [27]. BMAT has been historically known as yellow adipose tissue due to a moderate number of mitochondria that gives it a yellowish appearance. It is still unclear whether BMAT constitutes of a distinct population of adipocytes with mixed WAT and BAT phenotype or a heterogeneous population of both WAT- and BAT-type of fat cells. A gene expression profile of epididymal and bone marrow adipocytes shows significant difference in the expression of genes controlling biological processes and molecular functions including adipocyte differentiation, and lipid and carbohydrate metabolism. Interestingly, genes associated with brown adipocyte phenotype were over-represented in the bone marrow as compared to epididymal adipocytes [28]. Indeed, BMAT profile for white and brown adipocyte gene markers showed elevated expression of several BAT markers including PRDM16, FoxC2, PGC1α and Dio2. However, this profiling also showed low levels of UCP1 and β3AR, known BAT markers, and low levels of WAT markers including adiponectin and leptin (Fig. 1) [29]. Activation of PPARγ in bone marrow cells with a high affinity agonist rosiglitazone increased expression of Prdm16 and UCP1 indicating that progenitors of either brown or beige lineage are present in the bone marrow and can be mobilized in specific conditions [29].

Strong evidence suggests that at least some marrow adipocytes originate from the same Myf5 negative mesenchymal stem cells (MSCs) which can differentiate to osteoblasts and white adipocytes [30,31]. Indeed, the role of the transcriptional regulator and tumor suppressor retinoblastoma protein pRb in regulation of MSCs allocation to either osteoblast, brown, or white adipocyte lineages confirms a close relationship between all three types of cells and the possibility of interconversion between phenotypes [31,32]. Thus, a presence of pRb in early mesenchymal progenitors directs their differentiation towards osteoblasts, while an absence of pRb allows for commitment of the same progenitors to the beige adipocyte lineage and their further differentiation under the control of PRDM16. More interestingly, re-expression of pRb in cells already committed to the beige lineage converts them into adipocytes of white phenotype suggesting interconversion between white and beige phenotypes [31,32].

Perhaps an indication for metabolic type and function of marrow adipocytes may be suggested by their distribution in the marrow cavity. Studies on mice showed that BMAT may form two distinctive depots in the mice tibia (Fig. 2). One depot is juxtaposed to the trabeculae in proximal part of tibia bone, where active bone turnover takes place. Adipocytes in this location are randomly dispersed throughout the area. In contrast, fat in the distal part of tibia, where bone remodeling is practically absent, occurs as a very dense depot of adipocytes which form a ring adjacent to the bone endosteal surface (Fig. 2C). This distinctive pattern of fat accumulation may suggest a specific function for the adipocytes. One can speculate that adipocytes in proximal tibia may support bone remodeling by providing energy and cytokines, whereas fat accumulated in the distal part of tibia may consist of adipocytes that are rather metabolically inert or even have a negative effect on bone turnover.

Marrow fat may participate in lipid metabolism by clearing and storing circulating triglycerides, thereby providing a localized

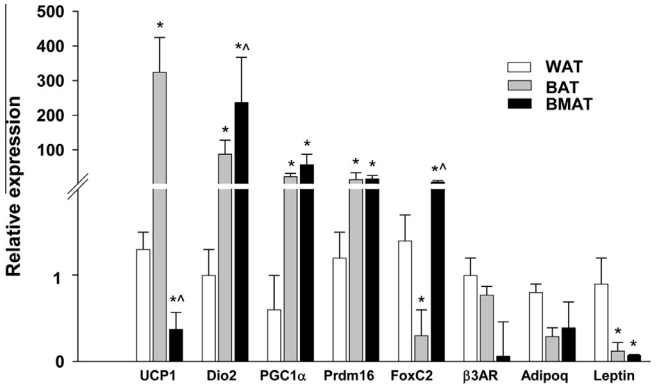

Fig. 1. Relative expression of adipocyte-specific gene markers in BAT and BMAT as compared to WAT [29]. RNA was isolated from epididymal WAT, interscapular BAT and bone marrow isolated from femora of 6 mo old C57BL/6 male mice ($n = 4$). Gene expression was analyzed using real time PCR and normalized to the level of 18S RNA in each sample. The values from bone marrow analysis were further normalized to the levels of FABP4/aP2 expression in WAT and BAT. $^{*}p < 0.05$ *vs.* WAT; $^{\wedge}p < 0.05$ BMAT *vs.* BAT.