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Metabolic Coupling between Bone Marrow Adipose Tissue and Hematopoiesis

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Abstract

Purpose of review—Mesenchymal stem cells (MSCs) located in bone marrow have the capacity to differentiate into multiple cell lineages, including osteoblast and adipocyte. Adipocyte density within marrow is inversely associated with bone mass during aging and in some pathological conditions, contributing to the prevailing view that marrow adipocytes play a largely negative role in bone metabolism. However, a negative association between marrow adipocytes and bone balance is not universal. Although MAT levels appear tightly regulated, establishing the precise physiological significance of MAT has proven elusive. Here we review recent literature aimed at delineating the function of MAT.

Recent findings—An important physiological function of MAT may be to provide an expandable/contractible fat depot, which is critical for minimization of energy requirements for sustaining optimal hematopoiesis. Because the energy requirements for storing fat are negligible compared to those required to maintain hematopoiesis, even small reductions in hematopoietic tissue volume to match a reduced requirement for hematopoiesis could represent an important reduction in energy cost. Such a physiological function would require tight coupling between hematopoietic stem cells and MSCs to regulate the balance between MAT and hematopoiesis. Kit-ligand, an important regulator of proliferation, differentiation, and survival of hematopoietic cells may function as a prototypic factor coupling MAT and hematopoiesis.

Summary—Crosstalk between hematopoietic and mesenchymal cells in bone marrow may contribute to establishing the balance between MAT levels and hematopoiesis.

Keywords

adipocyte; osteoblast; hematopoiesis; Kit-ligand; bone remodeling

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Introduction

Bone marrow is a hierarchal, self-renewing, and self-amplifying tissue maintained by small numbers of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). These cells have the capacity to self-renew asymmetrically and differentiate into specific cell lineages. The hematopoietic bone marrow is responsible for myelopoiesis, erythropoiesis, thrombopoiesis, and lymphopoiesis [1]. Hematopoiesis occurs in bone marrow in close contact with resident MSC-derived stroma that provides structural and functional support for HSC growth and differentiation [2, 3]. The stroma includes endothelial cells, smooth muscle cells, reticular cells, stromal fibroblasts, osteoblasts, and adipocytes [4]. HSCs and MSCs within bone marrow contribute to additional important physiological functions, including bone growth and turnover. Specifically, HSCs give rise to osteoclasts and MSCs give rise to endosteal osteoblasts [5, 6].

Marrow adipose tissue (MAT) refers to MSC-derived adipocytes located within the bone marrow niche. Although studied since the 19th century [7], efforts to understand the significance of MAT have increased substantially in recent years. MAT has a unique set of characteristics that set it apart from other fat depots. Spatially confined within the skeleton, expansion capacity of MAT is limited compared to visceral/subcutaneous white adipose tissue (WAT) and brown adipose tissue (BAT). While all adipose compartments are heterogeneous in their cellular composition, MAT differs from other compartments in that the adipocytes are interspersed at varying density throughout a heterogeneous population of cells that include HSCs and bone cells.

Differences among fat depots suggest unique functions. WAT depots serve primarily as sites of energy storage and adipokine secretion, and BAT depots serve as sites of basal and inducible energy expenditure [8]. The function of MAT is less certain. Here we review evidence that MAT provides a highly regulated expandable/contractible fat depot serving to minimize energy requirements for sustaining optimal hematopoiesis. Figure 1 summarizes this model. For additional perspectives on MAT, we direct the reader to recent reviews [9–13], including ones focusing on the relationship between MAT and energy metabolism [14], MAT and energy deficit [15], MAT and fatty infiltration of skeletal muscle [16], MAT and diabetes [17], MAT and exercise [18], and MAT and cancer metastasis [19, 20].

Adipocyte differentiation and MAT expansion

Local and systemic stimuli, which positively and negatively regulate lineage-specific signaling pathways, regulate MSC differentiation fate. The transcription factor PPARγ directs adipogenic differentiation through two phases: (1) determination, which converts MSCs to preadipocytes and commits them to the adipogenic lineage, and (2) terminal differentiation, in which the preadipocytes begin to acquire the necessary machinery for lipid transport and synthesis, and ultimately begin to accumulate lipids. In humans, MAT development and accumulation occurs in a physiologically sequential context driven by age, skeletal site, and gender. MAT development begins just after birth in the terminal phalanges and progresses to the distal and proximal long bones of the appendicular skeleton at an accumulation rate of approximately 10% per decade, so that by middle age, MAT occupies

50-70% of the total marrow volume, and represents approximately 5-10% of total body adipose tissue [21]. Men exhibit greater MAT volume than women up to middle age, but following menopause MAT volume in women becomes greater than in men [22]. In addition to the natural progression of MAT accumulation in healthy individuals, some pathological conditions, including postmenopausal, alcohol abuse, and disuse forms of osteoporosis, are associated with increased MAT accumulation.

Two locally distinct populations of marrow adipocytes have been described [23] and are commonly referred to as constitutive MAT (cMAT) and regulated MAT (rMAT) [24]. cMAT, also known as 'yellow' marrow, consists of densely packed adipocytes. In rodents, cMAT is common in caudal vertebrae, phalanges, and distal tibia and accumulates primarily as a function of age. In contrast, rMAT is interspersed in the red hematopoietic marrow of many bones and is more responsive than cMAT to physiological challenges [10, 24, 25]. rMAT adipocytes are reported to be smaller in size, and contain lower amounts of unsaturated lipids compared to cMAT and comparison of gene expression profiles suggests rMAT exhibits a transcriptional identity more similar to WAT [10, 24]. However, these observations may not offer a complete description of the range of MAT phenotypes, nor be universally generalizable. Hypophysectomy-induced growth hormone deficiency resulted in increased accumulation of triglycerides and cholesterol in femur diaphysis, presumably representing an increase in rMAT. However, in contrast to the aforementioned analysis [24], the increase in rMAT was associated with higher levels of unsaturated fatty acids (16:1, n-7, 18:2, n-6) with no change (16:0) or lower levels (18:0) of saturated fats [26]. It is clear that additional work is required to characterize the nature and physiological significance of the two or more locally distinct populations of marrow adipocytes.

MAT may exhibit a 'hybrid' phenotype (also referred to as beige fat) with characteristics shared with adipocytes in WAT and BAT [14]. Similar to WAT adipocytes, MAT adipocytes are large spherical cells that contain a unilocular lipid droplet. However, it is unclear the extent to which MAT is insulin sensitive, a defining characteristic of WAT. Compared to WAT, MAT adipocytes contain a greater number of mitochondria and higher level of expression of mitochondrial regulators such as PGC-1α and PRDM16. While this suggests a BAT-like phenotype, MAT does not express appreciable levels of the BAT marker UCP-1, suggesting that MAT adipocytes have limited ability to uncouple respiration [27]. In mice, *UCP-1* gene expression levels were 1×10^5 greater in BAT than tibia (Figure 2). Mild cold temperature stress due to room temperature housing (22°C) resulted in 5-fold increase in *UCP-1* gene expression in BAT and a non-significant 1.2-fold increase in femur compared to thermoneutral housing (32°C) [28]. These findings do not support an important role of MAT in non-shivering thermogenesis in mice, at least in the temperature range evaluated.

MAT development and accumulation is species-specific, and in mice typically occurs later in the life course compared to larger animals, including rats and humans. As described by Galileo Galilei in Dialogues Concerning Two New Sciences (published in 1638), bone size does not scale linearly with body size. In mice, the skeleton (including bone marrow) makes up a substantially smaller percentage of total body mass than in rats (10 times mouse mass) or humans (2×10^3 times mouse mass). Since hematocrit does not differ among these mammals, the hematopoietic capacity of bone marrow in larger animals is greater than in

smaller ones, which may provide a plausible explanation for differences in MAT accumulation among species. Mice are able to compensate for the inability of their small skeleton to support hematopoiesis during a physiological stress such as pregnancy by initiating extramedullary hematopoiesis [29]. Pathophysiological increases in bone volume fraction due to estrogen-induced osteosclerosis or juvenile onset osteopetrosis also induce extramedullary hematopoiesis in mice [30, 31]. Because mechanistic studies examining the function of MAT are often performed in mice, it is important to consider these species differences in hematopoietic capacity before extrapolating results to humans.

Does MAT regulate bone turnover balance?

MAT has generated considerable interest as a putative negative regulator of bone balance. Because adipocytes and osteoblasts differentiate from MSCs, increasing marrow adipocytes could reflect a shift in the differentiation program of MSCs from osteoblasts to adipocytes [32]. Mechanistically, inhibition of PPARγ decreases adipocyte differentiation while increasing osteoblast differentiation. Conversely, preosteoblast-targeted overexpression of PPARγ inhibits bone mass gain in male mice and increases ovariectomy-induced osteopenia in female mice [33]. On the other hand, it is uncertain whether physiological regulation of MAT levels requires changes in PPARγ gene expression [28]. Whatever the precise underlying molecular mechanisms, a shift in lineage decision to favor adipogenesis over osteoblastogenesis may prevent adequate coupling of bone formation to the prevailing level of bone resorption and result in a negative bone remodeling balance. Bone marrow adipocytes could also negatively influence bone metabolism by releasing adipokines. There is ample evidence that several of these (e.g., leptin, IGF-1 adiponectin, resistin) are capable of influencing bone cell differentiation [34]. Thus, factors produced by MAT could alter bone balance by (1) changing the rate of appearance of osteoblasts and/or osteoclasts onto bone surfaces, (2) increasing the rate of osteoblast and/or osteoclast disappearance from bone surfaces, or (3) altering osteoblast and/or osteoclast activity.

Some investigators have concluded that marrow adipocyte differentiation inevitably occurs at the expense of osteoblast differentiation and function, and that MAT represents a potential therapeutic target for interventions to prevent and/or treat osteoporosis [35, 36]. To challenge the hypothesis that increasing MAT negatively affects osteoblasts, Keune et al. [37] evaluated the impact of spaceflight-induced increases in MAT on osteoblast kinetics in rats. While spaceflight resulted in a 3.5-fold increase in MAT, there were no changes in osteoblast activity, lifespan, or production rate. This finding demonstrates that increasing MAT does not necessarily alter osteoblast dynamics. However, it is possible that failure to increase osteoblast number in response to increased bone resorption was due to diversion of MSCs from osteoblasts to adipocytes. Thus, this study does not rule out the possibility that increased MAT may have contributed to the negative bone turnover balance.

To address causality and efficacy of targeting MAT to prevent bone loss, Keune et al. [38] evaluated the skeleton in weight-bearing and hindlimb-unloaded WT and *Kit*$^{W/Wv}$ mice. Hindlimb unloading is a ground-based model for spaceflight and *Kit*$^{W/Wv}$ mice are MAT deficient. Osteoclast perimeter and bone formation were higher in distal femur metaphysis of MAT-deficient mice consistent with the concept that preventing MAT increases the

production of osteoblasts. However, cancellous bone volume fraction was unchanged in weight-bearing bones, and MAT-deficient mice exhibited exaggerated bone turnover and bone loss during hindlimb unloading. These results do not support the hypothesis that MAT accrual is responsible for disuse-induced bone loss in mice. Rather, they suggest that MAT attenuates disuse-induced osteopenia by dampening bone turnover.

The above findings and earlier work [39, 25] indicate that a negative association between MAT and bone mass is not universal and argue against indiscriminant suppression of MAT as a general strategy to prevent or treat osteoporosis. Perhaps a better understanding of how crosstalk between MAT and neighboring cells involved in regulating bone turnover may reveal conditions where purposely targeting MAT is justifiable.

Is MAT an endocrine target tissue?

MAT is an endocrine target tissue based on criteria that adipocytes in bone marrow respond to changes in circulating levels of hormones. Hormones derived from pituitary gland, adipose tissue, ovaries, adrenal gland, and pancreas influence MAT. The list of endocrine organs is likely to increase. To date, studies have focused on hormone deficiency and excess. The effects of physiological changes in hormone levels on MAT have received much less attention and should be a priority for future studies.

Growth hormone, leptin, and estrogen are examples of hormones that influence MAT levels. Growth hormone deficiency following hypophysectomy in rats, leptin deficiency in *ob/ob* mice, and estrogen deficiency following ovariectomy in mice and rats each lead to elevated MAT levels [40, 41, 26]. However, hypophysectomy, leptin deficiency, and ovariectomy also result in a plethora of metabolic changes that may obscure the specific effects of these hormones on MAT. Hypophysectomized rats, for example, become osteopenic, hypogonadal, hypophagic, hypoleptinemic, and have low IGF-I levels. Leptin-deficient mice have impaired bone growth, depressed growth hormone levels, are osteopetrotic, and become hyperphagic, diabetic and hypogonadal, while ovariectomized rodents experience accelerated bone growth, develop bone- and bone compartment-specific bone gain or loss, and become hyperphagic and hyperleptinemic. Conditions resulting in end organ resistance to growth hormone (e.g., alcohol abuse, skeletal disuse) can increase MAT without changing growth hormone levels [42, 43]. These findings suggest that hormones playing an important role in energy metabolism, reproduction, or bone biology are likely to influence MAT. However, the profound and often overlapping actions of these hormones on their target tissues also suggest that multiple hormones act in concert to regulate MAT.

While findings to date implicate growth hormone as a key regulator of MAT levels, the underlying mechanisms mediating this hormone’s action on bone marrow adipogenesis have received little attention. To better understand the role of growth hormone in regulating MAT and the impact of MAT on bone formation, Menagh et al. treated hypophysectomized rats exhibiting extensive fat infiltration into marrow with growth hormone, estrogen, IGF-I, or intermittent parathyroid hormone [26]. Intermittent parathyroid hormone is of interest because it is a potent stimulator of bone formation in the presence or absence of high MAT [39]. Whereas treatment with growth hormone normalized MAT levels without changing

leptin levels, treatment with either estradiol or IGF-I was ineffective in lowering MAT. A recent study suggests that intermittent parathyroid hormone directs bone marrow MSC fate to osteoblasts and away from adipocytes [44], a conclusion supported by an earlier study in calorically-restricted rats [45]. However, treatment of hypophysectomized or ovariectomized rats with intermittent parathyroid hormone, while dramatically increasing bone formation, did not alter MAT levels [46]. These divergent results suggest that bone anabolic interventions such as intermittent parathyroid hormone therapy may direct differentiation of MSCs towards osteoblasts without reducing existing MAT levels.

Administration of leptin, whether by intracerebroventricular or subcutaneous delivery, was effective in reducing elevated MAT levels in long bones of leptin-deficient *ob/ob* mice [47–49, 40]. The reduction in MAT was likely due to a combination of reduced adipocyte differentiation, increased fat oxidation, and increased adipocyte apoptosis [47–49, 40]. Evidence for a potent inhibitory effect of leptin on MAT received additional support from recent studies demonstrating that long-duration hypothalamic leptin gene therapy normalized MAT levels as well as body weight and most bone parameters in *ob/ob* mice fed normal and high fat diets [50]. The physiological actions of leptin on the skeleton occur at low hormone levels [51]. This could help explain why some studies fail to detect a relationship between blood leptin levels and MAT [52].

Is MAT an endocrine tissue?

Bone marrow adipocytes have the transcriptional machinery to generate and secrete a variety of hormones, cytokines, and growth factors. Thus, MAT has the potential to influence target cells in marrow and beyond through paracrine and endocrine signaling mechanisms. That being said, the specific functional role of MAT as an endocrine organ remains largely unknown due to two primary challenges: (1) assigning the contribution of MAT and extramedullary adipose depots to circulating adipokines, and (2) technical limitations related to a mixed cell population that confound accurate determination of MAT secretory profile. In Figure 2 we compare expression levels of adipokines (adiponectin, leptin, resistin, adipin and adipogenin) attributable to adipocytes among total tibia, BAT and WAT. Although expressed in tibia, expression levels for the adipokines were lower than in BAT or WAT, in part reflecting the relatively low MAT volume fraction in young adult mice. The lower gene expression levels do not support an important endocrine role for MAT under basal conditions. However, a recent report suggests that during caloric restriction, MAT-derived adiponectin significantly contributes to circulating levels of the hormone and exerts systemic metabolic effects at distant tissues such as muscle [53]. It remains to be determined how different conditions (e.g., obesity, aging, disease) influence the secretory profile, phenotype, and endocrine nature of MAT.

MAT and cold stress

Mice are typically housed at temperatures (18-23°C) well below thermoneutral for the species (~32°C) [54]. Mice are obligatory daily heterotherms and the resulting cold stress greatly increases sympathetic outflow to BAT and has profound effects on energy allocation. The requirement for adaptive thermogenesis to maintain body temperature results in

increased food consumption and important changes in body composition [28]. As pointed out by Overton [55], housing mice at sub-thermoneutral temperature alters nearly all physiological systems associated with the metabolic syndrome. A collateral impact of room temperature housing is premature cancellous bone loss. Housing mice at thermoneutral (32°C) prevented bone loss observed at 22°C and led to higher mineralizing perimeter and lower osteoclast-lined bone perimeter [28]. In addition to higher bone mass, there was a 2-fold increase in MAT; these findings should raise concern regarding interpretation of results in studies evaluating MAT in mice subjected to room temperature-induced cold stress.

MAT as a dynamic depot important for hematopoiesis

Hematopoietic lineage cells in bone marrow undergo continuous and very rapid turnover [56]. In a healthy human, ~35 billion bone marrow-derived blood cells are replaced/hr due to cell death. To place this number in perspective, osteocytes make up the majority of bone cells and the average adult human skeleton contains ~ 45 billion osteocytes [57]. These terminally differentiated osteoblasts have estimated average lifespans of ~25 years [57]. Thus, the daily turnover of osteocytes is negligible (~0.001%) compared to blood cells. It would require multiple lifespans for cumulative osteocyte turnover to equal a single day of hematopoietic cell turnover. As such, the high rate of exodus of hematopoietic lineage cells from bone marrow in conjunction with MAT expansion provides a plausible cellular mechanism for rapid replacement of hematopoietic cells by MAT.

Adding a typical adipocyte to mouse bone marrow (5.5×10^4 μm^3) displaces ~30 nucleated hematopoietic marrow cells. MAT volume increases gradually with age but can also change rapidly in response to metabolic, hormonal, and other perturbations (e.g., spaceflight). In Menagh et al. [26] described above, hypophysectomy increased MAT from ~5 to ~45% volume fraction in only 25 days and MAT was restored to normal levels within 10 days of initiation of growth hormone administration. These changes in MAT volume fraction could have resulted in displacement/replacement of more than 100,000 hematopoietic cells/mm^3 of bone marrow.

Role of c-kit signaling in coupling MSC and HSC differentiation and function in marrow

c-kit is a receptor tyrosine kinase. The ligand for c-kit has numerous aliases, including kit ligand, mast cell growth factor, stem cell factor, and steel factor. Alternative splicing results in membrane bound (m-kit ligand) or soluble (s-kit ligand) forms of the ligand which differ in their biological actions [58]. Interest in kit signaling as a putative pathway coupling MSC and HSC differentiation and function in bone marrow stems from the critical role of this pathway in hematopoietic lineage decision, cell proliferation, and cell survival [59], and the cellular distribution of c-kit and kit-ligand. With a few notable exceptions, c-kit expression is lost during HSC differentiation. The exceptions include (1) osteoclasts, which may play a role in mobilization of HSCs from their niche in bone marrow and (2) mast cells, which may play a role in regulation of adipogenesis [60, 61]. Cells derived from MSCs express m-kit ligand and s-kit ligand and osteoblast lineage cells may tether HSCs within the HSC niche, in part through m-kit ligand [62]. Considerable controversy surrounds the precise

organization of the hematopoietic niche and roles of cells that comprise the stroma. Nevertheless, it is well documented that cells derived from MSCs, including adipocytes, support hematopoiesis in vitro [63] and a recent study suggests that kit-ligand is critical to this function [64].

Loss of function mutations in c-kit receptor and kit-ligand can result in anemia, mast cell deficiency, altered body composition, and skeletal abnormalities. Mutations leading to global reduction in c-kit receptor function (e.g., $kit^{W/Wv}$) and m-kit ligand function (e.g., $kit^{Sl/Sld}$) in mice also result in absence of MAT in long bones and lumbar vertebrae [65]. A deficiency in kit signaling in mice prevents ovariectomy-induced increase in MAT and accentuates bone loss in hindlimb-unloaded mice [66, 38].

In addition to an absence of bone marrow adipocytes, kit receptor-deficient $kit^{W/Wv}$ mice have multiple abnormalities in fat metabolism, including hypertriglyceridemia, hypercholesterolemia, and elevated chylomicrons, low density lipoprotein, and very low density lipoprotein, indicating a defect in lipid transport into cells [67]. Additionally, the mutant mice have reduced lipoprotein lipase activity. These findings imply that kit signaling plays a role in lipid metabolism. Furthermore, receptor tyrosine kinase inhibitors targeting kit signaling, such as gleevec, have been reported to reduce blood glucose levels in patients with chronic myeloid leukemia and decrease body weight in rodents fed a high fat diet [68, 69]. In rats, MAT was 47% lower in gleevec-treated animals compared to controls due to reduced adipocyte density [70]. It is worth noting that gleevec treatment also reduced osteoblast-lined bone perimeter [70], an observation that further contradicts the assertion that drugs that decrease MAT will necessarily lead to an increase in osteoblasts.

$Kit^{Sh/Sh}$ mice have a mutation in a regulatory element leading to cell-specific loss of kit signaling. The mice are mast cell-deficient but in contrast to $kit^{W/Wv}$ and $kit^{Sl/Sld}$ are not anemic and have MAT, indicating that the absence of MAT is due to kit signaling insufficiency and not mast cell deficiency, per se [65]. Adoptive transfer of WT bone marrow into $kit^{W/Wv}$ mice was effective in replacing $kit^{W/Wv}$ HSCs with WT HSCs but, surprisingly, did not result in MAT infiltration [38]. It is not yet clear whether the absence of MAT in kit signaling-deficient mice is due to failure to form adipocytes or failure of adipocytes to accumulate lipids. In either case, $kit^{W/Wv}$ and $kit^{Sl/Sld}$ mice may provide models for investigating the physiological role of MAT.

Why does long-term fasting increase MAT?

At first glance, an increase in MAT with weight loss seems counterintuitive. However, taking into consideration the low energy cost of generating adipocytes and storing triglycerides compared to the high cost of maintaining hematopoietic bone marrow, thermodynamics should favor MAT formation. The energy cost of replacing hematopoietic cells leaving bone marrow with adipocytes is low. As mentioned, an average adipocyte occupies the same volume as ~30 nucleated bone marrow cells. During a prolonged fast, fat stored in WAT undergoes lipolysis, leading to increased circulating levels of fatty acids. Deposition of fatty acids released from WAT during fasting into MAT requires minimal energy expenditure. Once generated, the energy cost required to maintain MAT is low because of the large size

and low metabolic rate of individual adipocytes. The low energy cost of maintaining MAT contrasts with the high-energy costs required for the high metabolic rate and rapid turnover of hematopoietic cells (Figure 3); in contrast to simple incorporation of preformed lipids into fat, formation of hematopoietic cells requires continuous de novo synthesis of macromolecules. Fasting results in important adaptive responses that increase survival by reducing energy expenditure. Based upon the above considerations, we hypothesize that the increase in MAT initiated during fasting represents one such adaptation.

Evidence supporting a reciprocal relationship between MAT and hematopoiesis

Several lines of evidence support a tight reciprocal relationship between MAT levels and hematopoiesis. Normal aging is associated with an increase in MAT and a decrease in hematopoietic cellularity in humans [71, 72]. As mentioned, deficiencies in growth hormone, leptin, and estrogen all result in reversible increases in MAT. In each case, the increase in MAT is associated with decreased hematopoiesis. Furthermore, prolonged fasting, chronic alcohol abuse, and skeletal disuse (e.g., chronic bed rest, spaceflight) result in increased MAT and decreased hematopoiesis in humans or animal models. Importantly, age-related increases in MAT and decreases in hematopoiesis are reversed by cold temperature stress, blood loss, and infection [73–75] and enhanced by treatment with the PPARγ agonist troglitazone [76], providing circumstantial evidence supporting the concept that the prevailing requirement for hematopoiesis regulates MAT levels. Finally, Boyd et al. [77] recently reported that bone marrow failure associated with acute myeloid leukemia is due, in part, to leukemic suppression of bone marrow adipocytes. Specifically, the suppression of the adipocytes disrupts regulation of HSCs and progenitor cells, resulting in impaired myelo-erythroid maturation.

Conclusions

MAT is often inversely associated with bone mass, naturally fueling speculation that bone marrow adipocytes play a largely negative role in bone metabolism. Mechanistically, it has been hypothesized that differentiation to adipocytes at the expense of osteoblasts and/or adipocyte-derived adipokines lead to negative bone balance. According to this view, the plasticity of MSC differentiation is an attractive target for development of pharmaceutical interventions to suppress MAT and thereby increase bone formation. However, a negative relationship between MAT and osteoblasts is not universal and, when observed, causality has not been established. Taken together, the experimental evidence does not support the deterministic model where reducing MAT will invariably lead to increased bone volume.

An important physiological function of MAT may be to provide an expandable/contractible depot to minimize energy requirements for sustaining optimal hematopoiesis. If correct, there must be tight coupling between MSCs and HSCs to regulate the balance between MAT and hematopoiesis. The c-kit signaling pathway has emerged as an important component in this regulatory system. Future research directed toward understanding of crosstalk between MAT and hematopoietic lineage cells may lead to an improved understanding of MAT function relevant to human health.

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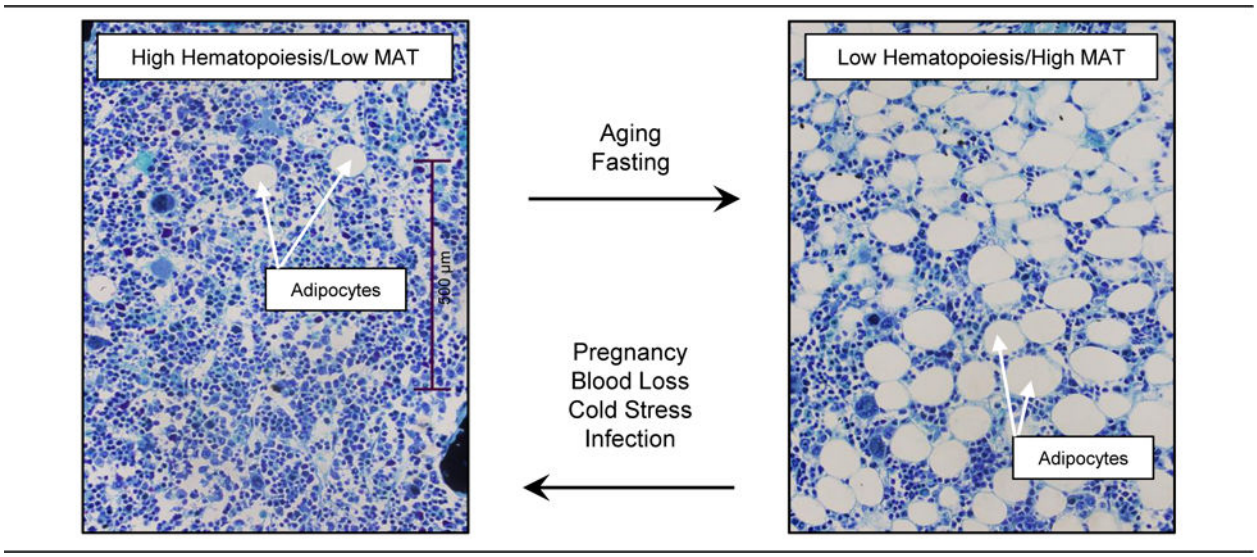

Figure 1. Putative role of MAT as an expandable/contractible fat depot to optimize the hematopoietic cell compartment

The reduced requirement for hematopoiesis with age results in a reduction in the hematopoietic compartment with a corresponding increase in MAT. Perturbations that increase hematopoiesis (pregnancy, blood loss, low temperature stress, and certain infections) increase the size of the hematopoietic compartment with a corresponding reduction in MAT. We hypothesize that increased MAT during fasting is an adaptive response signaled by negative energy balance. An increase in MAT and resulting reduction in hematopoietic compartment size during fasting would promote survival by lowering energy expenditure required to maintain unnecessary turnover of hematopoietic cells.

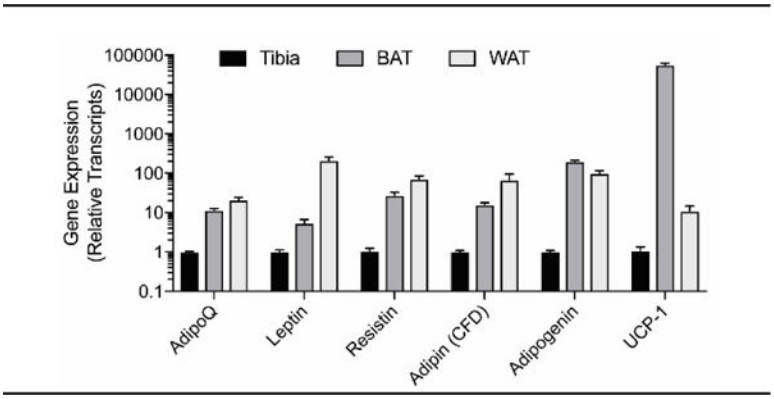

Figure 2. Relative gene expression of representative adipokines and *UCP-1* among fat depots in mouse

Adipokine expression levels in 4-month-old female B6 mice were 5 to 200-fold lower in total tibia (MAT) compared to expression levels in BAT and WAT. *UCP-1* expression levels in tibia were 10-fold lower compared to WAT and 100,000-fold lower compared to BAT. Values are mean ± SE, n=8/group.

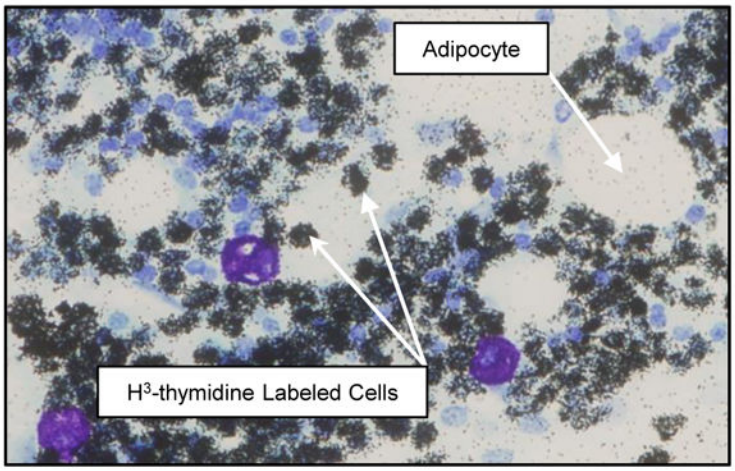

Figure 3. Illustration (using radioautography) of the rapid turnover of hematopoietic cells in bone marrow in rat tibia

A tracer level of H^3-thymidine was continuously infused for one week into a 6-month-old female rat using a subcutaneously implanted osmotic pump. The high labeling index indicates that the great majority of hematopoietic lineage cells passed through S-phase of the cell cycle during the one-week labeling interval. Label withdrawal studies (not shown) indicate that many of these cells experienced multiple rounds of proliferation during the labeling interval. Although one adipocyte would replace 30 nucleated hematopoietic cells, the majority of the energy savings following replacing hematopoietic marrow with MAT would stem from the differential in energy costs of maintaining the two tissues. Please note the size of the adipocyte and the potential for its displacing numerous hematopoietic stem cells.