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Development, regulation, metabolism and function of bone marrow adipose tissues

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Abstract

Most adipocytes exist in discrete depots throughout the body, notably in well-defined white and brown adipose tissues. However, adipocytes also reside within specialized niches, of which the most abundant is within bone marrow. Whereas bone marrow adipose tissue (BMAT) shares many properties in common with white adipose tissue, the distinct functions of BMAT are reflected by its development, regulation, protein secretion, and lipid composition. In addition to its potential role as a local energy reservoir, BMAT also secretes proteins, including adiponectin, RANK ligand, dipeptidyl peptidase-4, and stem cell factor, which contribute to local marrow niche functions and which may also influence global metabolism. The characteristics of BMAT are also distinct depending on whether marrow adipocytes are contained within yellow or red marrow, as these can be thought of as ‘constitutive’ and ‘regulated’, respectively. The rBMAT for instance can be expanded or depleted by myriad factors, including age, nutrition, endocrine status and pharmaceuticals. Herein we review the site specificity, age-related development, metabolic characteristics and regulation of BMAT under various metabolic conditions, including the functional interactions with bone and hematopoietic cells.

Keywords

BMAT; site specificity; development; regulation; bone; hematopoiesis

Introduction

Adipocytes are found in white (WAT) and brown adipose tissues, as well as in bone marrow adipose tissue (BMAT) and other more minor depots[1–4]. Although adipocytes were identified in human bone marrow more than a century ago, the origin, development, function and interaction of these adipocytes with other cells within bone marrow were largely

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unstudied until recently[3, 5]. BMAT develops in a distinct pattern throughout the skeleton and is dynamically regulated by a variety of physiological and pathological conditions. Herein we delineate the differences between bone marrow adipocytes (BMAs) within red and yellow marrow, which we have defined as regulated (r) and constitutive (c) BMAT, with rBMAT showing more dynamic responses to a variety of conditions. We also review the development and regulation of BMAT in human and rodents under physiological and pathological conditions, explore the local functions of BMAT related to osteogenesis and hematopoiesis, and compare the secretome and lipid composition of BMAT with that of more well-characterized white depots.

Development and regulation of BMAT in humans and rodents

Continual development of BMAT over the human lifespan

BMAT resides within the bone cavity together with hematopoietic cells, trabecular bone, nerve fibers, blood vessels and sinusoidal capillaries[6]. At birth, bone marrow is mainly composed of hematopoietic cells, and is thus known as red marrow due to color from erythroid cells. The number of adipocytes within bone marrow increases dramatically during postnatal growth, causing the bone color change from red to yellow. In general, expansion of BMAT occurs in a centripetal pattern, beginning in the distal skeleton of the hands and feet. Next, after development of BMAT in the epiphyses of long bones, conversion from red to yellow marrow continues in the diaphyses, which then progresses distally and proximally, with conversion occurring more rapidly at the distal ends[7]. By the age of 25 years, BMAT occupies 50 to 70% of total bone marrow volume[8] with red- to yellow-marrow conversion then continuing at a slower rate throughout the rest of life[9]. It should be noted that expansion of BMAT over the human lifespan is independent of WAT accumulation, since WAT peaks at middle- or early old age and then declines thereafter[10, 11]. BMAT in axial skeleton arises later than in long bones. In adults, BMAs are readily observed within red marrow of axial skeleton, including the sternum, ribs, pelvis and vertebral bones[2]. Within an individual, a gradient of BMAT is observed with development within the sacrum[12], and expanding proximally through the lumbar vertebrae[13]. The temporal replacement of red marrow by yellow marrow with age is shown in Figure 1.

Although the general patterning of BMAT development in humans occurs similarly between males and females, the absolute amount of bone marrow fat within vertebrae, sacrum and hips of adult males is higher than in age-matched females[12, 14, 15]. It should be noted, however, that vertebral BMAT rises sharply in women between 55 and 65 years of age, and is associated with menopause. Thus, in women older than 65 years, vertebral marrow fat content is ~10% higher than in males[16]. The rise in marrow fat content observed in postmenopausal females is secondary to estrogen deficiency and/or a reduced need for hematopoiesis following cessation of menstruation. Estrogen deficiency due to menopause (or ovariectomy) induces bone marrow adiposity, and also results in increased subcutaneous and abdominal WAT. Estrogen replacement reduces accumulation of BMAT in iliac crest by decreasing BMA size, and blocking the increase in BMA number[17]. Thus, in the adult and aged populations, differences in bone marrow adiposity between the sexes is largely

dependent upon estrogen, rather than testosterone, since the deficiency of testosterone in male mice has only mild effects on BMAT volume and gene expression[18].

Development of regulated and constitutive forms of BMAT in rodents

The development of BMAT in rodents generally follows the centripetal patterning observed in humans; however, distinctions between types of BMAs can be more readily observed in rats and mice than in larger species. We have built on the excellent work of Tavassoli[19, 20] to define two groups of adipocytes that are characterized, in part, by their location, how they are regulated, and their cellular properties. We have termed the BMAT within the yellow marrow of distal tibia and caudal vertebra constitutive BMAT (cBMAT). These adipocytes develop soon after birth and are readily observed by one week of age. By standard light microscopy, cBMAT appears essentially indistinguishable from WAT, with BMAs occupying the vast majority of the marrow space. As suggested by the term “constitutive” these cells are much more stable than the regulated BMAs (described below) in the face of a wide variety of nutritional, physiological or genetic interventions.

In rodents, rBMAT is located in the red marrow of tibia proximal to the fibula junction, in femur, and in axial skeleton[21, 22]. Development of rBMAT occurs later than cBMAT, with substantial development observed in C3H/HeJ mice by 12 weeks of age. The rBMAs are observed as single or clustered BMAs that are smaller than cBMAs, and are found interspersed with hematopoietic cells[3] (Figure 2). Development of rBMAT in long bones varies between mouse strains, and C57Bl/6J accumulate rBMAT in proximal tibia later than in C3H/HeJ mice[21]. Development of rBMAT in vertebrae is not observed within mice at baseline[8, 23], although marrow adiposity has been detected in lumbar vertebrae of obese *ob/ob* mice[22]. Marrow fat fraction and BMA number are also increased by ovariectomy in lumbar vertebrae[24, 25] and femur[24, 26] of adult rats, respectively. Our working model is that BMAT within rodent paws will be characterized as cBMAT, whereas that within radius and humerus will mainly be rBMAT. Whereas human adult males generally have more BMAT than premenopausal females [14, 15], adult female mice appear to have more rBMAT in tibia than males[18, 21, 27]. In contrast, cBMAT in distal tibia is similar between sexes[18, 21, 27]. As in humans, estrogen deficiency in rodents is a strong stimulus for BMAT development[18, 28], and whereas ovariectomy increases cBMAT of distal tibia by ~30%, the expansion of proximal tibial rBMAT is far more extensive[18, 28]. Estrogen is not only necessary to restrain accumulation of BMAT, but exogenous administration of estrogen is sufficient to stimulate rapid loss of marrow adiposity in tibia[29].

In addition to aging and estrogen depletion/replacement[18, 28, 29], rBMAT of rodents is also regulated by many nutritional, environmental, genetic, and endocrine factors. For instance, three weeks of cold exposure stimulates a dramatic and specific decrease in size and number of rBMAs in proximal tibia[21]. Other specific negative regulators of rBMA size or morphology include fasting[30], intracerebral[31] or subcutaneous[32] leptin, intraperitoneal β_3-agonist[33], acute myeloid leukaemia[34], exercise[35] and lactation[36], some of which will be discussed in detail later within this review. Although development of rBMAT is independent of the lipodystrophy gene caveolin-1 (*Cav1*), accumulation of rBMAs in proximal tibia is largely dependent on expression of another lipodystropy gene, cavin-1(*Ptrf*)[21]. In addition to

showing dynamic depletion of marrow adiposity, rBMAT is also subject to expansion in response to a variety of conditions. For example, mice with high fat diet-induced obesity show much higher osmium staining of proximal tibial marrow lipid than lean mice. Elevated lipid in proximal tibia is due to an increase in both BMA number and size[35, 37, 38] (Figure 2). In contrast, neither bone marrow lipid nor the size/number of BMAs is different in distal tibial cBMAT of lean and obese mice (Figure 2). Importantly, overeating of a standard laboratory chow diet also increases rBMAT in rodents with a genetic predisposition for hyperphagia[32, 39, 40]. Thus, it is the positive energy balance and/or development of obesity that contributes to rBMAT expansion, rather than dietary composition. Expansion of rBMAT is also observed in response to thiazolidinediones[41], glucocorticoids[42], fibroblast growth factor-21[43], type 1 diabetes[44] and type 2 diabetes[41, 42], and as discussed below, caloric restriction[45–47]. Whether these disparate signals causing BMAT expansion result in BMAs with similar molecular and physiological characteristics remains unknown.

Exercise

Mice with access to a wheel will voluntarily run ~10 km per day[35, 48]. This level of exercise reduces rBMA number and size in both lean and diet-induced obese mice[35], suggesting that energy stored within marrow adipocytes is readily mobilized under these conditions. A possible mechanism for rBMA depletion is the specific induction (in whole tibia) of perilipin 3, which has been linked to increased basal lipolysis and β-oxidation. Importantly, perilipin 1 (and 5), which is more effective than perilipin 3 at repressing basal lipolysis, remains unchanged by exercise[35]. In addition, exercise partially offsets the induction of rBMAT by a peroxisome proliferator-activated receptor γ (PPARγ) agonist[48].

Caloric restriction

Whereas exercise causes loss of both rBMAT and WAT[35, 49], these adipose depots are not uniformly correlated. A particularly interesting divergence is observed in the case of caloric restriction. Despite decreasing subcutaneous and visceral WAT[50], caloric restriction (e.g. 30%) causes a dramatic expansion of rBMAT, an observation observed in humans through to rodents[45, 51]. Expansion of BMAT with caloric restriction contributes to the elevated circulating concentrations of adiponectin[45]. Although the mechanistic bases for effects of caloric restriction on BMAT remain unknown, a potential cause is increased circulating glucocorticoids[27], which have been shown to increase marrow adiposity and decrease bone mass[52]. Peripheral or intracerebral administration of leptin decreases rBMAT volume[31, 32], and leptin administration blocks the increase in rBMAT with calorie restriction[53]; however, rabbit and rodent data suggest that reduced endogenous leptin concentrations can be dissociated from the BMAT expansion[27]. The disparate effects of calorie restriction on development and/or metabolism of BMAT and WAT provide compelling evidence that BMAs are developmentally and metabolically distinct from white adipocytes.

As described above, cBMAT is largely resistant to stimuli that positively or negatively influence rBMAT; however, this tissue is not immune to moderate expansion (~30%) in response to calorie restriction[27] or thiazolidinedione treatment[41]. Furthermore, cBMA number is modestly depleted by a prostaglandin E_2 receptor type 4 agonist in ovariectomized rats[25]. Although not measured in rodents, it appears likely that both rBMAT

and cBMAT are reduced in response to profound starvation[54], blood-letting[55], leukemia[34], and infection[56]. Thus, whilst the term “constitutive” as a descriptor of some BMAT depots has merit, there are also caveats that diminish its dogmatic applicability.

Functional interactions between BMA and other cells within the bone marrow niche

BMAT is undoubtedly an important component of the bone and hematopoietic niches; however, the specific relationships between BMAs and osteoblasts/osteoclasts, and hematopoietic cells have not yet been well-defined in a mechanistic manner. Bone, hematopoietic cells, and BMAT are contained within a closed system, and thus expansion of one of these populations is often at the expense of one or both of the others. Although this reciprocal relationship undoubtedly holds true at the extremes, regulated changes in extracellular fluid volume and cell size may act to buffer the tightness of this ‘zero-sum’ relationship[57].

Bone

Support for a reciprocal relationship between BMAs and bone cells comes from innumerable clinical and animal studies, which generally demonstrate an inverse correlation between BMAT content and bone mass[9, 28, 51]. This inverse relationship may be driven in part by mesenchymal progenitors having a cell fate choice between BMAs and osteoblasts. Thus, signals that promote adipogenesis (e.g. thiazolidinedione[58], dexamethasone[52] and fibroblast growth factor-21[43]) impair osteogenesis, whereas signals that inhibit adipogenesis (e.g. Wnt10b signaling[59, 60]) promote differentiation of osteoblasts. Although reciprocal regulation of mesenchymal cell fate may explain the expansion of BMAT and reduction of bone mass with age[9], the specific proteins and signaling pathways involved have not been delineated. In addition, BMAs *per se* may secrete factors that repress osteogenesis since *in vitro* co-culture of osteoblast progenitors with either primary adipocytes or fully-differentiated 3T3-L1 adipocytes decreases activity of alkaline phosphatase, and expression of the osteogenic transcription factor, runt-related transcription factor-2[61]. Adipogenic cells also secrete factors *in vivo* that inhibit bone repair[62]. In this regard, expression of dipeptidyl peptidase-4 in marrow appears to be specifically from adipogenic progenitors and production increases in distal tibial cBMAT of aged animals. Dipeptidyl peptidase-4 impairs osteogenesis in cultured cells, whereas *in vivo* administration of dipeptidyl peptidase-4 inhibitors accelerates fracture healing[62]. Finally, BMAs may also contribute to bone loss by stimulating osteoclast differentiation and activation. For example, in the absence of parathyroid hormone receptor signaling, BMAs secrete receptor activator for NF-κB (RANK) ligand to increase osteoclast activity and bone resorption[63]. The marked induction by dexamethasone of RANK ligand from BMAs suggests a potential mechanistic link between the chronic use of synthetic steroids and bone loss[64]. On the other hand, evidence has also accumulated that this inverse relationship between BMAT and bone mass, whilst compelling, may not always be causally linked. For instance, in the absence of BMAT, ovariectomy still causes bone loss in *c-kit* deficient mice[28]. Similarly, bone loss is also observed in type 1 diabetic mice in which expansion of BMAT is blocked by a PPARγ inhibitor[65], or leptin administration[66], and leptin injection to calorie restricted mice

decreases BMAT without influencing loss of trabecular and cortical bone[53]. Lastly, certain inbred strains of mice also indicate that the inverse relationship is not universal in that C3H/HeJ mice have both high proximal tibial rBMAT and bone mass, whereas C57Bl/6J mice exhibit low values for both of these variables[21].

Hematopoiesis

Consistent with the closed system discussed above, expansion of BMAT is also generally associated with depletion of hematopoietic cellularity, and *vice versa*. Naveiras *et al*[23] suggests that BMAs have an overall net negative effect on hematopoietic cells. They compared the red and yellow marrow of the thorax and caudal vertebrae, respectively, and observed reduced number and cycling capacity of hematopoietic stem cells and progenitors in the presence of BMAT. In the absence of BMAT, whether by genetic (e.g. A-ZIP/F1[67]) or pharmacological (e.g. PPARγ inhibitor) means, the reconstitution of hematopoietic progenitor cells and recovery after transplantation was improved[23], and favored selective expansion of myeloid and granulocyte populations[23]. The inverse relationship between BMAT and hematopoietic cellularity may be due, in part, to BMAs competing for space within the marrow cavity. Consistent with this idea, in irradiated mice, implantation of hematopoietic stem cells with adipogenic progenitors or preadipocytes results in reduced regeneration of the hematopoietic stem cell population, perhaps due to increased numbers of BMAs[62].

In contrast, work by other investigators suggests a supportive role for BMAs in function of hematopoietic cells. For example, in *vitro* co-culture of Lin^- blood cells with adipocytes increased numbers of hematopoietic progenitors and development of mature granulocytes[34]. Furthermore, in the context of leukemia, regeneration of healthy erythroid progenitors and granulocytes after irradiation was improved in mice in which BMAT was expanded by treatment with a PPARγ-agonist[34]. Importantly, the specific secretion of stem cell factor by BMAs, but not white adipocytes, is required in caudal vertebrae for maintenance of hematopoietic cells[68]. Although BMA-derived stem cell factor is not required for creation of blood cells in non-irradiated mice, the absence of stem cell factor impairs the ability of hematopoietic stem cells from femurs/tibiae and caudal vertebrae to reconstitute donor cells after irradiation. Indeed, knockout of stem cell factor in adiponectin-CRE expressing cells diminishes survival of mice after irradiation and bone marrow transplant[68]. Whereas adiponectin is well-known to have positive effects on hematopoietic stem cell activation and hematopoietic recovery following irradiation or chemotherapy[69, 70], the relative importance of secretion from BMAs versus WAT depots remains unknown. It should be noted, however, that at least in the case of caloric restriction, BMAT is an important and disproportionate source of circulating adiponectin[45]. In summary, although one might imagine the reciprocal relationship between BMAs, bone cells and hematopoietic cells to be characterized by mutual antagonism, interactions between BMAT and other cell types within the marrow niche are more complex than this, and many positive (or independent) effects have also been observed.

A limitation of studies exploring interactions between BMAT and hematopoiesis is that they largely depend upon irradiation and bone marrow transplantation. Interestingly, irradiation,

itself, causes a profound wave of marrow adipogenesis in humans[71] and rodents[72]. Regulated BMAs after irradiation are largely derived from resident precursors that were positive for adiponectin expression[68]. Further evidence that BMAT expansion derives from recipient precursors comes from the absence of BMA expansion in lipodystrophic A-ZIP/F1 mice irradiated and transplanted with wildtype bone marrow cells[23]. Both of these studies suggest that irradiation-induced BMAs are generated from recipient precursors rather than from donor cells. Interestingly, without irradiation, transplanted mesenchymal progenitor cells homed to marrow and developed into many of the BMAs observed in older recipient mice[73].

Elevated secretion of a subset of adipokines by BMAT

There is no evidence from gene profiling or expression studies that any of the myriad adipokines secreted from WAT are not also expressed by BMAT[74, 75]. However, differences in relative expression and/or secretion of proteins from WAT and BMAT exist, and likely reflect the distinctive functions and properties of each depot. For example, leptin is well-known to be expressed in proportion to adipocyte size[76]. Thus, whilst the mRNA for leptin is reported to be reduced (or unchanged) in BMAs[45, 74], this may simply reflect the smaller size of these cells, and the fact that BMAs show only modest hypertrophy in the face of positive energy balance[35, 38]. In addition, secretion of RANK ligand from BMAs has local effects on osteoclasts[63, 77]; however, production of RANK ligand is not specific to BMAs and has also been documented from WAT[78]. Whilst a recent report provides compelling evidence that stem cell factor is expressed by BMAs but not by visceral white adipocytes[68], other investigators report detectable expression of the stem cell factor gene, *kitl*, within WAT and brown adipose tissues[79]. Inspection of GEO datasets also provides support for detectable expression of *kitl* in adipose tissues and cultured adipocytes, and suggests that expression of *kitl* in white adipocytes is similar to that in bone marrow adipocytes[74]. Finally, elevated secretion of adiponectin is observed from BMAT, despite expression levels of *adipoq* being similar or lower in BMAT compared to WAT[45, 74]. With caloric restriction, circulating adiponectin increases, despite a loss of WAT, due to expansion of BMAT and the disproportionate contribution that elevated secretion makes[45, 47]. Thus, in this case it appears that BMAs may have a mechanism for expressing certain secreted proteins at high levels relative to white adipocytes, despite similar or even lower levels of mRNA.

Unsaturated lipid composition of cBMAT

The distinct lipid composition of BMAs isolated from red and yellow marrow was first identified in rabbits by Tavassoli *et al* in 1977[80]. He reported that "*shifts from myristic and palmitic acids (in red marrow) to their respective monounsaturated derivatives myristoleic and palmitoleic acids (in yellow marrow) were found*." These findings generally hold true from humans to rodents[21]. Humans have an increased unsaturation index in bone marrow of distal tibia compared to hip, and lipid unsaturation is higher in isolated rat adipocytes from distal tibia and caudal vertebrae cBMAT compared to adipocytes isolated from rBMAT or subcutaneous WAT[21]. Consistent with these observations, expression of stearoyl-CoA desaturases-1 and -2 mRNAs, which encode key enzymes that catalyze formation of monounsaturated fatty acids, is much higher in cBMAs than in subcutaneous white

adipocytes[21]. Although the physiological relevance of higher unsaturated lipids in BMAT is unclear, clinical studies demonstrate that a lower proportion of BMAT unsaturation is associated with reduced bone mineral density and increased risk of fracture in postmenopausal women[81, 82].

Summary and future directions

It has become clear that BMAT is distinct from other well-characterized adipose depots, such as WAT and brown adipose tissue. In addition to its unique location, BMAT also differs with regards to origin, development, site-specific regulation, cellular character, and function. Although inverse relationships are generally observed between BMAT, bone mass and hematopoietic cellularity within the closed environment of bone, recent mechanistic work sheds light not only on antagonistic interactions, but also highlights numerous positive, supportive interactions between BMAs, and bone and hematopoietic cells. As animal models are developed and/or advanced technologies are applied to the study of BMAT biology, we anticipate rapid advances in our understanding of BMA precursors and development, the genetic and metabolic characteristics of BMAT and WAT, and the interactions between BMAT and other cell types within the bone marrow niche. Translation of these results will improve our understanding and treatment of human diseases affecting bone and blood cells, and may provide therapeutic targets to influence whole body metabolism.

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Abbreviations

BMAT	bone marrow adipose tissue
BMA	bone marrow adipocyte
WAT	white adipose tissue
cBMAT	constitutive BMAT
rBMAT	regulated BMAT
RANK ligand	receptor activator for NF-κB ligand
PPARγ	peroxisome proliferator-activated receptor gamma

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Highlights

1. BMAT expansion develops in a centripetal pattern during human and rodent lifespans.
2. Amount of regulated BMAT changes dynamically in response to a wide variety of conditions. Constitutive BMAT is more stable.
3. Local interactions between BMAT and cells of the marrow niche are complex and require further investigation.
4. Proteins secreted from BMAT mediate functional interactions with cells near and afar.

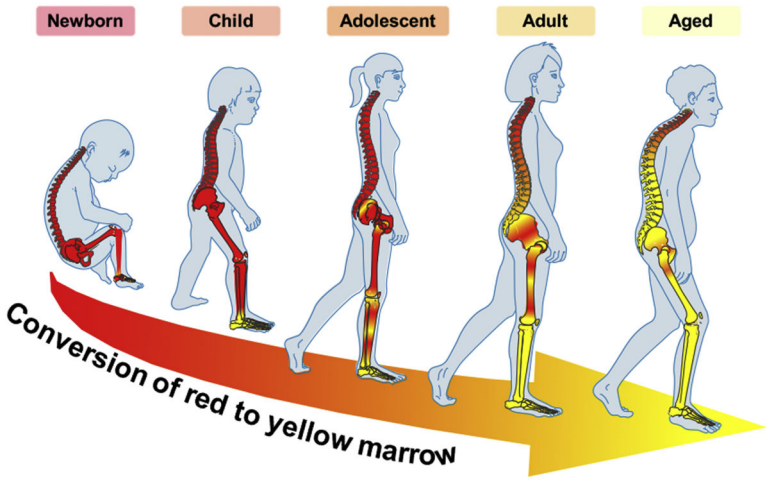
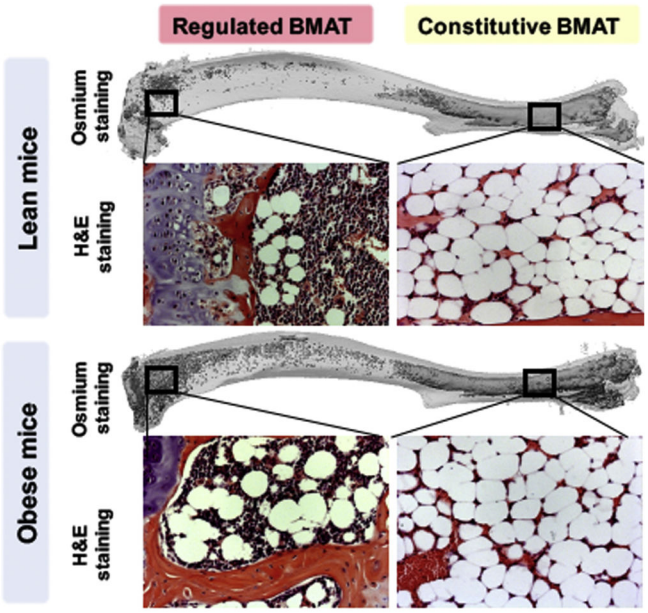


Figure 1. The conversion of red to yellow marrow during aging

Throughout life, hematopoietic cells are gradually replaced by adipocytes within bone marrow. This conversion of red to yellow marrow begins early in life and generally occurs in a centripetal pattern, beginning in the distal bones. Accumulation of bone marrow adipocytes in elderly people is associated with development of osteoporosis. Original elements used in this diagram are from Servier Medical Art (http://smart.servier.com/).



Specificity	Regulated BMAT (rBMAT)	Constitutive BMAT (cBMAT)
Locations	e.g. Proximal tibia, femur, lumbar vertebrae	e.g. Distal tibia, caudal vertebrae
BMA size	~500μm²	~1000μm²
BMA distribution	Dispersed in red marrow	Densely packed in yellow marrow
Regulation	Wide-ranging control of expansion and contraction	Relatively stable

Figure 2. Location and characteristics of mouse tibial BMAT

Tibiae from 20-week-old mice were decalcified, lipid stained with osmium tetroxide, and BMAT then detected by microcomputed tomography. H&E staining shows the histological difference between proximal rBMAT and distal cBMAT within tibiae. The properties of rBMAT and cBMAT are summarized in the table[21].