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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, regulation and metabolic characteristics of BMAT under various metabolic conditions, including the functional interactions with bone and hematopoietic cells.

1. 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 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.

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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2. Development and regulation of BMAT in humans and rodents

2.1. 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 the color from erythroid cells. The number of adipocytes within bone marrow increases dramatically during postnatal growth, causing the bone color to 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 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

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proximally through the lumbar vertebrae [13]. The temporal replacement of red marrow by yellow marrow with age is shown in Fig. 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].

2.2. 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 as 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 adipocytes that are smaller than cBMAs, and are found interspersed with hematopoietic cells [3] (Fig. 2). Development of rBMAT in long bones varies between mouse strains, and C57Bl/6 J mice 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 in 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 tetroxide staining of proximal tibial marrow lipid than lean mice. Elevated lipid in proximal tibia is due to increase in both BMA number and size [35, 37, 38] (Fig. 2). In contrast, neither bone marrow lipid nor the size/number of BMAs is different in distal tibial cBMAT of lean and obese mice (Fig. 2). Importantly, overeating of standard laboratory chow diet also increases

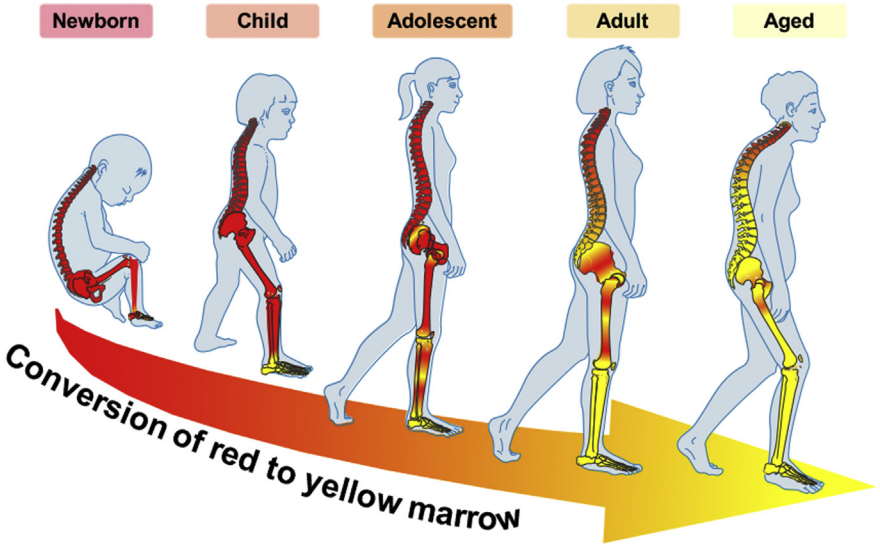

Fig. 1. The conversion of red to yellow marrow during aging. Throughout life, hematopoietic cells are gradually replaced by adipocytes within bone marrow. This conversion of red to yellow marrow begins early in life and generally occurs in a centripetal pattern, beginning in the distal bones. Accumulation 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/).