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Bone marrow adipocyte tissues: An overview

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Abstract
Adipose tissue found in bone marrow has received a lot of interest lately. It serves as a source of energy as well as vital immunological, paracrine, and endocrine functions. BMAT (bone marrow adipose tissue) is a heterogeneous tissue that is primarily present in the iliac crest, vertebrae, and the medullary canal of the long bones (tibia, femur, and humerus). Age-related adipogenesis in bone marrow cavities can also be a symptom of diseases such diabetes mellitus type 1 (T1DM), type 2 diabetes, anorexia nervosa, oestrogen and growth hormone deficiency, decreased haematopoiesis, and osteoporosis. Impaired bone health is linked to higher marrow fat levels. Greater marrow fat has been linked to circulating lipids, growth hormone changes, visceral obesity, and hypoleptinemia. This study tries to explain the composition, control, and origin of bone marrow fat. Preadipocyte factors like the crucial transcription factors CCAAT/enhancer binding protein alpha or beta (C/EBP alpha or beta) and peroxisome proliferator-activated receptor gamma (PPAR gamma) are in charge of forming bone marrow adipose tissue. Bone fragility, which is mostly brought about by decreased bone mass and increased bone marrow adipose tissues, is one of the most significant side effects of high BMAT. To fully understand BMAT's intended role and to exploit it as a therapeutic target for conditions like diabetes, more research is required.

Keywords: Bone marrow adipose tissue, PPARγ, C/EBPα or β, bone fragility

Introduction
The medullary canal of the long bones (tibia, femur, and humerus), as well as the vertebrae and iliac crest, are the main locations for the complex, heterogeneous tissue known as mammalian bone marrow (BM). Numerous cell types, including hematopoietic and mesenchymal cells, differentiate in the bone marrow (BM) from the most immature stem cells to fully developed, functioning cells. This comprises bone cells such osteocytes, the most developed population of osteoblast lineage cells present in bone matrix, and osteoblasts, the cells that produce bone. The genesis of these cells is mesenchymal. Hematopoietic cells, primarily myeloid, lymphoid, and erythroid hematopoietic precursors, are found in the bone marrow along with differentiated cells like osteoclasts, which break down bone, red blood cells, B and T lymphocytes, macrophages, megakaryocytes, and natural killer cells. (Horowitza *et al*., 2017) [8].

A multitude of induction signals and ageing both cause the number of TBM adipocytes to increase. Adipose tissue has essentially been divided into three categories: white (WAT), brown (BAT), and beige adipose tissue. BMAT is derived from skeletal lineages and regulates whole-body energy metabolism as well as bone marrow homeostasis. [Youmna *et al*., 2015; Nuttall *et al*., 2014] [23, 16]. The iliac crest, vertebrae, and medullary canal of the long bones (tibia, femur, and humerus) are the main locations for BMAT (Bone Marrow Adipocyte Tissues), a heterogeneous tissue. The processes that give rise to bone marrow and bone, respectively, are osteogenesis and haematopoiesis. Age-related adipogenesis in bone marrow cavities can also be a symptom of diseases such diabetes mellitus type 1 (T1DM), type 2 diabetes, anorexia nervosa, oestrogen and growth hormone deficiency, decreased haematopoiesis, and osteoporosis. (Piotrowska *et al*., 2021) [17].

Bone marrow adipose tissue
BMAT is being given more attention since it makes up between 50 and 70 percent of the marrow volume and is a crucial component of the marrow microenvironment. MAT (Marrow adipose tissue) and yellow adipose tissue are other names for this type of fat. (Piotrowska *et al*., 2021) [17]. It makes up roughly 5-10% of the total mass of fat in adult, healthy, lean humans (Fazeli *et al*., 2013) [6].

"Yellow" fatty marrow, which replaces "red" marrow in humans and mice with age and late in life in other skeletal areas like the spine, is caused by the growth of BM adipocytes. (Moerman *et al*., 2004 and Moore *et al*., 1990) [12, 15].

Marrow adipose tissue - origin and differentiation

The majority of specialists concur that bone marrow (BM) adipocytes, which are more closely related to osteoblasts than other cells of mesenchymal origin, are produced by mesenchymal stem cells (MSC). (chondrocytes, myocytes, and marrow stromal cells). [Horowitz *et al*., 2017] [8] Osteoblast development necessitates the expression of Osterix1 (osx1), a transcription factor that is expressed right after Runx2. An early arrest in osteoblast differentiation is caused by osx1 deletion. In general, MAT content rises with age and is least in the long bones and vertebrae of young animals, including humans (Horowitz *et al*., 2017) [8]. Greater MAT is associated with a greater fracture rate in mice on calorie-restricted diets and in young women with anorexia nervosa. (Fazeli *et al*., 2013) [6]. Long bones contain adipocytes that develop from mesenchymal stem cells, and there is strong evidence that MAT and osteoblasts originated from the same early progenitor. But there is also proof that adipocytes can develop from a variety of progenitors with various cell surface characteristics. (Horowitz *et al*., 2017) [8].
There are currently accepted to be at least three different types of adipocytes-white, brown, and beige-based on their appearance, function, and origin. (Lynes *et al*., 2018) [10].

Classification of Adipose tissue

- White adipose tissue: Classic large
- Lipid droplet-rich cells
- Classical methods of storing and releasing fatty acids, in particular using a variety of lipases to regulate lipolysis.
- 99% of subcutaneous and visceral adipose tissue (VAT) depots are made up of white adipocytes. Brown Adipoose tissue: Small, Multilocular.
- Mitochondria-rich cells.
- Capable of uncoupling energy by burning fatty acids and releasing heat in response to sympathetic tone activation.
- Beige adipose tissue: In the subcutaneous and inguinal depots, beige adipocytes coexist with traditional white adipocytes and exhibit some functional characteristics of brown cells, particularly in terms of their capacity for thermogenesis via uncoupling protein.
- The marrow adipocyte may actually be an osteoblast with a sizable lipid droplet, according to numerous researchers. (Robles *et al*., 2019) [18].

Basic Anatomy of the "BMAT"

BMAs develop loosely attached and dispersed among hematopoietic cells, in contrast to subcutaneous or visceral fat lobules made up of 80% tightly packed adipocytes. Such adipocyte distribution may not be considered a true "adipose tissue" in that sense. rBMA are typically found at the trabecular location where bone remodelling is active, which supports their involvement in this process, whereas cBMA constitute a relatively dense adipocyte area. (Hardouin *et al*., 2016) [7]. The primary transcriptional regulators PPAR and c/EBP are traditionally involved in a transcriptional cascade that controls the adipogenesis of resident MSC (mesenchymal stem cells) in the bone marrow. (Hardouin *et al*., 2016) [7].
Adipogenesis is widely regarded as a process that competes with osteoblastogenesis within the BM. Increased osteoblastogenesis or adipogenesis are caused by haplo-insufficiency or overexpression of PPAR in BM progenitor cells, respectively. (Sadie-Van *et al*., 2013) [20].
BMA-enriched areas are thought to have reduced vascularization and decreased perfusion, as shown in the hip of participants who are of normal age (Budzik *et al*., 2014) [2].
The vascularization of the cBMA and rBMA regions may also differ, with startlingly higher capillary densities in the cBMA sections of mice. (Roche *et al*., 2012) [19].
Adipogenesis is constrained by factors that promote osteogenesis, such as mechanical pressures, growth hormone, or insulin-like growth factor 1 (IGF-1); conversely, osteoblastogenesis is constrained by factors that promote adipogenesis, such as oxidative stress, immobility, and increased glucocorticoid levels. (Nuttall *et al*., 2014; Abdallah *et al*., 2012) [16, 1].
This tissue was long thought to serve only as a filler for the medullary canals of long bones (such as the tibia, femur, and humerus), which are involved in the transformation of red (haematopoietic) bone marrow into yellow (non-haematopoietic) bone marrow. By the third decade of a person's life, it gradually builds up in the marrow cavity and covers the whole trabecular bone of the femur, tibia, and vertebrae. (Fazeli *et al*., 2013, Moore *et al*.,1990) [6, 14].
In both rodents and humans, there are two distinct subtypes of BM adipocytes: constitutive BMAT (cBMAT/cMAT) and regulatory BMAT (rBMAT/rMAT) (Suchacki *et al*., 2018) [21]. The development of rBMAT/rMAT occurs throughout life and is found in active haematopoietic locations such the mid- to proximal tibia, femur, and lumbar vertebrae. After birth, cBMAT/cMAT quickly develops in the caudal vertebrae and distal tibia. These two populations differ significantly in a number of significant ways: Similar to WAT, rBMAT/rMAT adipocytes have lower amounts of the adipogenic transcription factors Cebpa and Cebpb and more saturated fatty acids than cBMAT/cMAT adipocytes. [Suchacki *et al*., 2018] [21].
According to study, higher BMAT is brought on by adipogenesis and an increase in adipocyte population rather than an increase in adipocyte size when calories are restricted. The uncoupling of BMAT and energy metabolism may happen as a result (Cawthorn *et al*., 2014) [3].

Regulation

Due to the gonadal-pituitary axis's endocrine feedback, decreasing oestrogen levels are accompanied by rising follicle-stimulating hormone (FSH) levels. According to a recent study by Rosen Annu, using a polyclonal antibody to prevent the FSH ligand from interacting to its receptor stopped the increase in MAT following ovariectomy (Liu *et al*., 2017) [9]. Additionally, administration of this antibody reduced MAT volume in mice that underwent a sham operation. The authors demonstrated that the FSH receptor is expressed by both adipocytes and mesenchymal stromal cells and that increased mesenchymal stromal cell adipogenesis occurs in mice lacking the FSH receptor, which suggests that postmenopausal-elevated FSH is a factor in the increased adipogenic differentiation of the skeletal stem cell. Recent research from the Icelandic AGES cohort showed a significant positive correlation between circulating FSH and MAT volume. A large Chinese cohort showed similar results.

(Z. Cheng, personal communication) (de Paula *et al*., 2020) [5]. In times of calcium deficiency, parathyroid hormone promotes bone resorption by controlling the amounts of calcium in the blood. On the other hand, irregular bursts of parathyroid hormone (PTH) can stimulate the production of bone by encouraging skeletal stem cells to differentiate into osteoblasts and drawing osteoblast progenitors from perivascular and bone lining cells. As seen in caloric-restricted mice and rats, PTH also inhibits marrow adipogenesis in the latter scenario. (Turner *et al*., 2011; Maridas *et al*., 2019) [22, 11].

Conclusion:

In conclusion, during the course of an individual's life, the marrow adipocyte is a special cell that is innately programmed for various functions that are time and space-specific. In order to influence hematopoiesis and osteogenesis, marrow adipocyte progenitors are positioned inside the skeletal space at different phases of differentiation. By having a common ancestor with osteoblasts, the marrow stem cell, mature marrow adipocytes and osteoblasts are related. The intricate regulation of skeletal or mesenchymal stem cells that leads to their development into marrow adipocytes or osteoblasts is influenced by neuronal and endocrine inputs as well as a vast network of paracrine/autocrine modulating factors. It is now understood that the proportion of osteoblasts to adipocytes determines a person's maximal bone mass. The preservation of marrow homeostasis depends on this equilibrium as well as general health, endocrine function, and dietary status.

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