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Bone marrow adipocytes – Good, bad, or just different?

Ananya Nandy, PhD[a,b], **Elizabeth Rendina-Ruedy, PhD**[a,b,c,+]

[a]Department of Medicine, Division of Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232; USA

[b]Center for Bone Biology, Division of Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232; USA

[c]Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN 37232; USA

Bone -- what was once considered a static tissue which passively supports and protects soft tissues, continues to prove to be an excited tissue harbouring a milieu of cells within its medullary microenvironment of the marrow space. In its simplest form, ‘bone’ is remodelled throughout life once every 10 years, meaning the skeleton you had a decade ago has been completely replaced by new bone. Of course, this is a general approximation and other factors contribute to the rate at which bone is replaced along with the quality of bone, but nonetheless, bone is an incredibly dynamic tissue. While much focus and therapeutic treatment regimens have targeted primary bone cells including bone resorbing osteoclasts, bone forming osteoblasts, and the mechano-sensing osteocytes, the field is beginning to shift its attention towards the complex and diverse populations of secondary cells within the skeletal niche.

Aside from the mineralized bone tissue, the bone marrow itself is composed of a highly heterogeneous mixture of stem and progenitor cells of hematopoietic and mesenchymal lineage, which can give rise to a multitude of cells from macrophages and blood cells to osteoblasts, chondrocytes, and adipocytes. While much attention has been focused on these cell types, it’s only been within the past decade that we have begun to appreciate the unique characteristics of the bone marrow adipocyte. It is therefore the goal of this edition of *Best Practices* to present what is currently known about bone marrow adipocytes, including their stem cell lineage and functional relevance, while also providing an outlook for continued future research for these novel cells.

Bone marrow adipocytes were first described in 1898 by Ralph Stockman as he investigated how arsenic impacted bone marrow and blood (1). These early images are remarkable as they exquisitely depict histological sections on bone marrow with distinct “fat cells” (1). From this time, it took an additional 50 years until more literature became available describing bone marrow adipocytes in mice, rats, rabbits, dogs, and humans (2). But it began

[+]Denotes corresponding author.

to be more frequently referenced in the literature only in the 1980's (3). Fast forward over 120 years from the initial observation by Stockman, and it is with great enthusiasm that this collection presents recent studies and the up-to-date understanding of bone marrow adipocytes, along with future clinical perspectives related to this unique depot.

Collective accumulation of bone marrow adipocytes within the marrow cavity are referred to as bone marrow adipose tissue (BMAT or MAT). Remarkedly, BMAT constitutes over 10% of total body fat in lean and healthy adults (4) representing 50-70% of the total bone marrow cavity (5,6). Initially thought to be inert space-fillers, recent studies have confirmed the contribution of BMAT in a varying range of physiological as well as clinical aspects. Once identified, observational studies began to report that BMAT is often inversely associated with bone mineral density (BMD). For example, this relationship has consistently been demonstrated during aging (7,8), post-menopausal osteoporosis (8,9), anorexia nervosa (10), as well as during obesity (11-13). In these scenarios, patients often present with an increase in BMAT along with a decrease in bone mass or BMD (14,15). This relationship also holds true under various therapeutic treatments such as chemotherapy, radiotherapy, and glucocorticoid administration which are all associated with a decrease in BMD accompanied with the expansion in BMAT (7,16). Therefore, while BMAT currently provides no clinical prognosis, these initial correlational studies were integral in providing a bird's eye view of how these depots could potentially influence its intimate neighbour, bone. In the following chapters, Bredella and colleagues have highlighted how BMAT is imaged clinically, with exquisite details about current options and their limitations, along with providing an outlook to future prospective for clinical imaging. Given these limitations highlighted in this section, it is true much of what we have learned relative to BMAT in health and disease has come from more invasive techniques using preclinical models. Li and MacDouglad masterfully describe various rodent models commonly used to study BMAT while providing a comprehensive evaluation of methods used to detect and quantify bone marrow adipocytes.

Intuitively, recent exploration has been to categorically compare bone marrow adipocytes to other more commonly studied adipose depots including white adipose tissue (WAT) and brown adipose tissue (BAT). Unlike BAT, which is multilocular containing large number of small lipid droplets and mitochondria (17), both WAT and BMAT are unilocular with a single large lipid droplet and very little cytosol (18-20). However, BMAT differs from both WAT and BAT in many aspects. First, WAT primarily originates from progenitor cells in lateral plate mesoderm (21) during the second semester of gestation (22) and is present in subcutaneous and visceral (abdominal cavity and around all major internal organs) adipose tissue depots. While BAT is originated from Myf_5^+ progenitor cells (22) and is majorly located in the supraclavicular region and neck (23). Indeed, like other more classic depots of adipocytes, bone marrow adipocytes are also derived from mesenchymal stromal cells (MSCs). Although, all the molecular players involved in the final fate determination of these stromal cells have yet to be identified, important regulators have been reported including transcriptional regulation via peroxisome proliferator-activated receptor gamma (PPAR-γ). Notably, while bone marrow adipocytes express many markers similar to classic white adipocytes, these cells also express osterix (Osx or *Sp7*), which is generally restricted to early progenitor cells of the osteoblast lineage (24). Finally, impressive work has recently been performed identifying a novel precursor population within the bone marrow

termed marrow adipocyte lineage precursors (MALPS) (5). These cells have been shown to demonstrate adipocyte genes and are committed to adipocytic lineage (i.e., osteoblast markers are absent), but interestingly, do not express genes related to lipid metabolism (5). What controls this lineage fate, and can it be manipulated for therapeutic potential? This edition hopes to highlight these regulators in subsequent chapters and expand on factors such as sclerostin, a Wnt inhibitor, adipokines including leptin and adiponectin, sex hormones (estrogen and follicle stimulating hormone or FSH), as well as parathyroid hormone (PTH) (25-28).

As the bone marrow adipocyte lineage and regulation continues to be investigated, focus within the field is shifting to determine the precise molecular and physiological function of BMAT, which remains largely unknown. Due to some of the overlapping characteristics between the extensively studied WAT and BAT, logical inferences can be generated. For example, given the presence of the large lipid droplet within bone marrow adipocytes, one would assume that these cells too have the exquisite ability to store lipid precursors (i.e., fatty acids), and possibly, the ability to release these substrates to adjacent cells given the appropriate stimulus. While this has in fact been demonstrated in an *in vitro* system (29,30), the physiological implications for such a phenomenon remains underappreciated. Tencerova, Kassam, and colleagues elaborate on what is known and/ or speculated related to the metabolic functions of bone marrow adipocytes and how they impact adjacent cells.

Once more highlighted is that BMAT remains distinct in their functionality as well. Recent studies have shown that unlike WAT, BMAT remains relatively unresponsive to β3-adrenergic stimulus dependent lipolysis (31). As such, even under acute fasting bone marrow adipocytes do not undergo lipolysis, which creates a unique scenario whereby lipids stored in BMAT are not available as energy substrates for adjacent tissues during starvation (31). Indeed, this sheds light on the well documented observation of BMAT expansion in patients with anorexia nervosa despite loss of peripheral adipose depots but presents even more mystery around their precise role in physiology. The chapter within this collection from Scheller et. al, expands on these observations by providing an expert review on the neuronal innervation of bone marrow adipocytes using state-of-the-art techniques mastered in their lab.

Additional clues relative to BMAT's function have come from a recent comparative proteomics study. This study demonstrated that while fatty acid, glucose, and PPAR-α regulated metabolism were enriched in WAT, cholesterol biosynthesis, sphingolipid signalling, and arachidonic acid metabolic pathways were highly enriched in BMAT, further indicating differential lipid metabolism between these two tissues (4). Finally, elegant PET/CT analyses have shown BMAT has very low capacity of insulin induced glucose uptake due to lower expression of genes involved in this pathway (32). Interestingly, however, BMAT demonstrates a markedly higher ability to take up glucose at basal levels compared to WAT (32). Therefore, it is reasonable to define BMAT as a generally insulin-resistant tissue, which does not experience the classic starvation-induced lipolytic stimulation observed in other adipose depots, while also demonstrating a differential lipid profile. It's important to note that these functional studies have been published within the past two years, further underscoring the need for continued investigation in this area.

Aside from BMAT's role in 'normal' physiology and its impact on resident cells, bone marrow adipocytes have even been documented to impact cancer cells as well. To this end, Edwards and colleagues explore the relationship between BMAT and multiple myeloma (MM). From these studies the correlation between obesity and MM remain strong, and provide the tenant that marrow adipocytes provide energy substrates, act as a source of adipokines, and even secrete exosomes containing mircoRNAs, all of which promote the progression of MM.

As this is a highly active and promising area of research, ground-breaking studies continue to emerge, further strengthening the importance of bone marrow adipocytes in health and disease. The following chapters will present a comprehensive overview of the novel aspects of BMAT along with emphasizing the most up-to-date research. This collection concludes with a succinct summary of this collection by Dr. Clifford Rosen, a pioneer in the field bone biology, marrow adiposity, and endocrinology. While it is tempting to underestimate all the intricacies that present when studying bone marrow adipocytes, it is clear that these cells provide a wealth of information related to the skeletal niche and integrated physiology. In closing, where do we stand --are bone marrow adipocytes good, like BAT, or bad, much like WAT? Our simple response is that they are different, but stay tuned.

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