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Bone Marrow Adipose Tissue: The First 40 Years

Beate Lanske and **Clifford Rosen**

Harvard School of Dental Medicine, Boston, MA

Maine Medical Center Research Institute, Scarborough, Maine 04074

Clifford Rosen: cjrofen@gmail.com

The bone marrow is the only organ in mammals in which bone and fat tissue reside side-by-side. Intriguingly cells from these two tissues arise from the same mesenchymal progenitor, yet their functions are quite distinct. Moreover, their morphologic appearance would never betray their common origin. The degree of intimacy between bone and fat cells is unique among tissue types, and as such their relationship begs for a clear interpretation, not just to complete our understanding of the marrow niche, but also because there may be therapeutic implications. In the past decade the number of publications directly related to bone marrow adiposity has increased more than five fold although it should be noted that some are review articles or opinion pieces. This reflects the relatively slow progress in understanding some of the basic tenets that underlie the development and function of marrow adipose tissue. Notwithstanding, now is a great opportunity to look back at some of the original observations concerning marrow adiposity and its relationship to bone, in order to better gauge our progress and to look forward to the challenges that lie ahead.

Marrow adipose tissue was first described by anatomists in the late 19th century. These scientists painstakingly characterized all types of normal and pathologic tissues. Some of the earliest observations were reported in individuals who died of arsenic poisoning where fat infiltration was extensive and was associated with a paucity of hematopoietic elements[1]. Those observations were buried for fifty years until the relationship of adipocytes to blood cells was re-examined in the latter half of the 20th century. The advent of chemotherapy for hematologic disorders led to bone marrow biopsies after treatment. These often revealed extensive fatty infiltration with few red or white cells. Similarly patients with aplastic anemia and myelofibrosis were reported to have a related marrow adiposity phenotype[2] Subsequent reports noted an inverse relationship of bone marrow adipocytes to hematopoiesis. This led pathologists to hypothesize that fat infiltration was a ‘filler’ that occupied space reserved for hematopoietic stem and progenitor cells. Others postulated that the presence of fat cells was a default mechanism that resulted from stress on the marrow. Nevertheless, the concept that the marrow is ‘space-limiting’ has persisted and has re-emerged as new studies on bone marrow adiposity have been undertaken.

In contrast to hematologists, bone biologists were late to studying constituents of the bone marrow. In 1964, Emery and Follett took advantage of the practice of taking the second toe at autopsy for routine histology at the Sheffield Children’s Hospital and assessed bone marrow adipose tissue (BMAT) within small bones from the toes of two groups of neonates, i.e., those born at term and premature fetuses[3]. They reported that fatty change in the

marrow begins, in many cases, before full term (40 weeks). Among 43 full-term infants fewer than 1/3 showed no fat replacement. Moreover, the authors detected MAT in the toes of children born as early as at 28 weeks of gestation and observed that the increment in MAT was more marked between 6 and 10 weeks after birth[3]. In the small bones of the toe, the process of fat replacement was very advanced by 8 months of life, and at the age of 1 year the marrow cavity was completely filled with fat. The study also allowed the authors to determine that premature birth did not change the time course of MAT development in that part of the skeleton. Thus in appendicular bones, the development of MAT begins in the distal portion of bones and represents a preserved process shared by different vertebrates (e.g., mice, rats, rabbits and humans).

It took one of the great pioneers of bone biology, Pierre Meunier, working in Lyon 45 years ago, to first describe the replacement of bone marrow elements with fat from iliac crest biopsies of adult patients with osteoporosis[4] Meunier hypothesized that it was the osteoporotic condition itself that led to replacement of bone marrow with fat. It wasn't long however before a controversy arose that was related to the definition of fat in the marrow. Some had proposed that marrow adiposity represented lipid droplets but not true adipocytes. Others considered these lipid droplets to be true white adipocytes. It took more recent studies with the advent of lineage tracing to resolve that controversy and define a true 'marrow' adipocyte' rather than an ectopic lipid droplet. On the other hand, the inverse relationship between bone and fat, originally noted by Meunier, has been repeatedly confirmed over the last 2 decades, not only from bone biopsies but also by in vivo MRI and dual energy CT imaging[56].

In 1976, Tavassoli began the process of characterizing marrow adipocytes and delineated their morphologic features[7]. Tavassoli identified two distinct populations of adipocytes, one present within the red marrow and the other populating the yellow marrow. Only the former stained positively with Performic acid-Schiff (PFAS) and disappeared when hematopoietic tissue expanded in response to experimentally induced hemolysis. In those circumstances, PFAS-negative adipocytes of yellow marrow lingered. Early in life, yellow marrow was structurally arranged as a dense grouping of cells similar to white adipose tissue in other depots, occupying the distal part of small bones of the hands and feet. Later, adipocytes were presumed to fill both the long bones and the vertebrae, and these cells were acid-Schiff positive. Interestingly, Tavassoli also was the first to note adipogenic and gelatinous infiltration of the marrow with starvation[8]. Forty years later Scheller and colleagues confirmed this observation by describing two types of marrow adipocytes in rodents, 'constitutive', i.e. from birth and located in the distal extremities and tail vertebrae, and 'regulated' located more proximally and adjacent to hematopoietic marrow but capable of expanding and contracting in response to environmental and nutritional stimuli[9]. Those authors also went on to define in rodents, distinctions in insulin sensitivity between the two types of marrow fat. They also described unique differences in the extent of marrow adiposity among inbred strains of mice.

In sum, seminal observations from a half-century ago still provide us with an important road map to further characterize bone marrow adipose tissue (BMAT) and its relationship to bone remodeling. Indeed there has been progress in this area of investigation within the last two

decades. But, we should also note what we don't know about BMAT so that the reader can judge the true extent of progress.

Several aspects of BMAT physiology and pathogenesis are now established. **First** and foremost, bone marrow adiposity is a physiologic process that begins at or before birth and proceeds inexorably in the appendicular skeleton and ultimately in the vertebrae, replacing hematopoietic tissue[10]. **Second**, BMAT is composed of adipocytes that are lipid laden and stain positive for perilipin[11]. These cells are not ectopic lipid droplets and do not reflect excess fat that is deposited outside of conventional adipose depots. **Third**, BMAT is dynamic and responsive to nutritional, environmental and hormonal stimuli[1213]. It can expand in response to a high fat diet or calorie restriction[14]. Endocrine signals strongly influence the extent of BMAT in syndromes such as estrogen withdrawal, absence of PTH signaling, or glucocorticoid excess[12,15]. In some circumstances the gain in BMAT is directly related to expansion of peripheral adipose tissues, but in other circumstances, such as anorexia nervosa and some lipodystrophies, the reverse is sometimes found[1617]. **Fourth**, marrow adipocytes can express markers of both bone and fat cells[181920]. For example, marrow adipocytes trace with Prrx1 and Sox9, early mesenchymal makers, but also with Osterix, or Sp7, once considered an osteoblast specific transcription factor[2115]. As such, although both osteoblasts and adipocytes can express common transcriptional factors, a divergence in the differentiation scheme beyond the earliest mesenchymal progenitor could lead to mesenchymal cells with distinct functions[22] In that vein, Fan et al reported that marrow adipocytes but not peripheral adipocytes express and secrete RANKL[15]. To complicate the cellular phenotype further, Westendorf and colleagues noted that in an osteoblast specific conditional mouse with deletion of HDAC3, more than 10% of the 'presumed' marrow adipocytes also stained positively for Runx2 and contained perilipin positive lipid droplets[23]. **Fifth**, excess BMAT is often but not always associated with uncoupled turnover. In many of the conditions associated with infiltration of marrow adipocytes, the bone-remodeling unit is uncoupled such that resorption is increased and bone formation is suppressed. These include aging, Type I Diabetes Mellitus, rosiglitazone exposure, anorexia nervosa and others[2425,26]. Almost certainly stromal cell fate is altered in these conditions and there is a shift towards adipogenesis. On the other hand, the increase in resorption has been related to enhanced Pparγ expression leading to higher expression of osteoclastic differentiation markers, although recently that tenet has also been challenged[2728]. Other factors certainly must be important, including the adipocytic expression of cytokines that could directly mediate osteoclastogenesis. **Sixth**, marrow adipocytes secrete adipokines that can affect whole body metabolism. Cawthorn and colleagues demonstrated that adiponectin secretion is very high from the bone marrow in some conditions in which there is increased BMAT (e.g. anorexia nervosa and post chemotherapy)[14]. It is uncertain if this occurs in other disorders or if other adipokines are also generated by marrow adipocytes. **Seventh** the phenotypic characterization of high BMAT does not always imply skeletal loss or fragility. For example, in C3H/HeJ, an inbred strain of mice, bone marrow adiposity is markedly higher, yet bone formation and bone mass are very high[293031]. Similarly the loss of BMAT does not immediately translate into greater bone mass. In the lactating B6 mouse, bone marrow adiposity declines while bone loss is occurring[32]. And during cold exposure, mice lose both bone mass and BMAT[33].

So there has been some progress, particularly in BMAT phenotyping and the use of osmium microCT to quantitate whole bone adiposity in mouse models, but many questions remain. For example, **first** we still do not know the origin of the marrow adipocyte. Certainly Osterix (Sp7) marks waves of early progenitor cells that could ultimately become an adipocyte or osteoblast[34]. In addition, virtually all peripheral fat cells label with PDGFRa, an early progenitor marker, although data in marrow adipocytes is not as convincing[35]. Morrison and colleagues demonstrated that the presence of the leptin receptor on mesenchymal progenitor cells in the marrow is an early indicator of the marrow adipocyte particularly with diet-induced obesity[36]. However, others have suggested, but not proven, that the bone lining cell (BLC) or a pericytic cell lining the vasculature, could differentiate into an adipocyte. These hypothesis may be tenuous because of our previous inability to fully characterize the BLCs and pericytes. On the other hand, Kalajzic et al have for the first time identified genes expressed on DMP positive bone lining cells[37]. This breakthrough may lead to further characterization of cells within the niche that could give rise to the marrow adipocyte. **Second**, we do not understand the nature of the marrow adipocyte in regards to its response to fuel homeostasis. Why would a marrow adipocyte trap fatty acids in both states of starvation and diet induced obesity? Does BMAT exist as a reserve for the struggling osteoblast, or another depot that can store fat during periods of excess substrate? Work from Donahue and colleagues in hibernating marmots provide novel insights, particularly into the lipases that may be active in the marrow adipocyte during fuel deficient states[38]. **Third**, and importantly, we believe that the marrow adipocyte is unique in its characteristics, but what function would a distinct adipocyte have in the marrow niche. It is clearly established that the site of origin of adipocytes plays a huge role in its subsequent function (e.g. visceral vs subcutaneous fat) but it is less clear what function the marrow adipocyte plays in niche homeostasis. Moreover, although some ‘beige’ like genes are expressed in mature marrow adipocytes, there is very little evidence to suggest that these cells are thermogenic[39]. Intuitively, one might consider the appendicular skeleton as having lower temperatures and therefore need a source of heat to maintain the niche, but we have no functional evidence to support that tenet, and some contrary data that in states of ‘beiging’ in other depots (e.g. cold), the BMAT does not express UCP1 protein of become multilocular[39].

Fourth, if increased marrow adiposity in the vertebrae is associated with greater fracture risk, what is the mechanism? We don’t believe enhanced BMAT in the long bones impacts skeletal strength, although not all the data are in since femoral MRI spectroscopy in humans has only been available for a few years. On the other hand it is intriguing that vertebral MRI has identified a very strong inverse relationship with bone mass and fracture risk. Is it conceivable that compressive forces on the vertebrae may lead to greater fragility in the presence of marrow adiposity? Or is this a function of greater bone resorption and enhanced uncoupling in the remodeling sequence? We have no data to argue one way or the other, but what we have learned is that BMAT is very location specific and that function may also be distinct at various locations.

We have attempted to delineate both the progress and the challenges in respect to our understanding of marrow adiposity. The advent of greater technology for lineage tracing, for

imaging, and for sorting marrow adipocytes promise to provide new insights into this novel area of bone biology.

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