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REVIEW

SPECIAL ISSUE: CELL BIOLOGY OF THE IMMUNE SYSTEM

Bone marrow adipose cells – cellular interactions and changes with obesity

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ABSTRACT

The bone marrow is a spatially restricted niche, housing cells of the hematopoietic and mesenchymal lineages in various hierarchical commitment states. Although highly localized, cells within this niche are also subject to regulation by environmental and/or circulatory changes through extensive vascularization. Bone marrow adipocytes, derived from mesenchymal stem cells and once known as marrow space fillers, are a heterogeneous population. These cells reside in distinct niches within the bone marrow and interact with proximal cells, such as hematopoietic precursors and lineage-committed cells. In this diverse cellular milieu, bone marrow adipocytes influence commitment decisions and cellular lineage selection by interacting with stem and progenitor cells. In addition, bone marrow adipocytes respond to environmental changes, such as obesity, by undergoing hypertrophy, hyperplasia or adoption of characteristics resembling those of peripheral brown, beige or white adipocytes. Here, we review recent findings and concepts on the influence of bone marrow adipocytes on hematopoietic and other cellular lineages within this niche. We discuss how changes in local, systemic, cellular and secreted signals impact on mesenchymal stem cell expansion, differentiation and lineage commitment. Furthermore, we highlight that bone marrow adipocytes may be intermediaries conveying environmental cues to influence hematopoietic cellular survival, proliferation and preferential differentiation.

KEY WORDS: Bone marrow adipocyte, Bone marrow cellularity, Hematopoiesis, Obesity

Introduction

The hollow spaces inside the skeletal system of the body are filled with a soft, spongy and gelatinous tissue called the bone marrow, which makes up ∼4% of the total body weight of an average adult (Hardouin et al., 2016). The bone marrow is composed of hematopoietic and mesenchymal stem cells (HSCs and MSCs, respectively) as well as their progenitor cells at various differentiation and lineage-committed states. There are two types of bone marrow: (1) the hematopoietically active red marrow, and (2) the adipose tissue-filled yellow marrow (Fig. 1). At birth, all the bone marrow is hematopoietically active and therefore appears red due to the abundance of hemoglobin. By early adulthood, 40% converts into adipose tissue-filled marrow, which appears yellow due to the carotenoid in fat droplets (Guillerman, 2013). Red-to-yellow marrow conversion is a normal maturation process during which the fat content of bone marrow increases from 40% to 80% and vascularization decreases (Guillerman, 2013). By early adulthood, when maximal bone density is reached, total bone marrow adipose tissue (MAT) makes up ∼70% of the mass within all bone marrow cavities and 10% of the total body adipose tissue mass (Fazeli et al., 2013; Scheller et al., 2016). The remaining hematopoietically active red marrow is highly vascularized and contains diversely interacting cellular networks, which includes bone marrow adipocytes (BMAs), along various niches.

Here, we outline the idiosyncratic nature of MAT and the communication with other cell lineages within the bone marrow. We highlight the fate of HSCs and MSCs in the bone marrow and define the cellular interactions in spatially distinct niches of the bone marrow. Importantly, we discuss the unique properties of BMAs compared with peripheral adipocytes and the influence of obesity on BMAs and the changes to cell populations in the bone marrow.

Regional specific areas of the bone marrow have distinct cellularity

Advancements in microscopy such as intra-vital, whole-body optical and two-photon microscopy, as well as single-molecule fluorescence coupled with methods of *in vivo* optical trapping have allowed for better visualization of a single HSC in live bone marrow (Askenasy et al., 2003; Lo Celso et al., 2009; Köhler et al., 2009; Xie et al., 2009). Using these multimodal techniques, Lassailly et al. discovered physical and functional heterogeneity in regionally specific areas of the bone marrow with diverse cellularity (Lassailly et al., 2013). They showed that HSCs can either reside in the endosteal zone (inner lining of the bone) or in the sinusoidal zone (central marrow). Interestingly, to maintain hematopoietic homeostasis, the cells within the two zones must maintain communication (Guerrouahen et al., 2011; Rosen et al., 2009) (Fig. 2).

Endosteal zone cellular interactions

The endosteal zone is at the inner lining of the bone where osteoclasts, osteoblasts and MSCs reside to maintain bone homeostasis. A population of long-term HSCs (LT-HSCs) localizes to this region by sensing high Ca^{2+} concentrations due to osteoclast-mediated bone resorption (Adams et al., 2006) (Fig. 2). Once there, their interaction with spindle-shaped N-cadherin^{+} CD45^{-} osteoblasts keeps LT-HSCs in a quiescent state for long-term storage, both through cell-associated receptor binding and soluble factors (Zhang et al., 2003; Sarkaria et al., 2018). The binding of integrin α4β1 on osteoblasts to vascular cell adhesion protein 1 (VCAM1) on LT-HSCs reduces their apoptosis (Frisch et al., 2008) and secreted chemokines C-X-C motif ligand 12 (CXCL12) and angiopoietin-1 work together to induce quiescence (Fig. 2) (Arai et al., 2004; Tzeng et al., 2011). Furthermore, osteoblasts appear to play a role in LT- and short-term HSC (ST-HSC) recovery by regulating proliferation through Notch signaling, as a rise in osteoblast content has been associated with an increased

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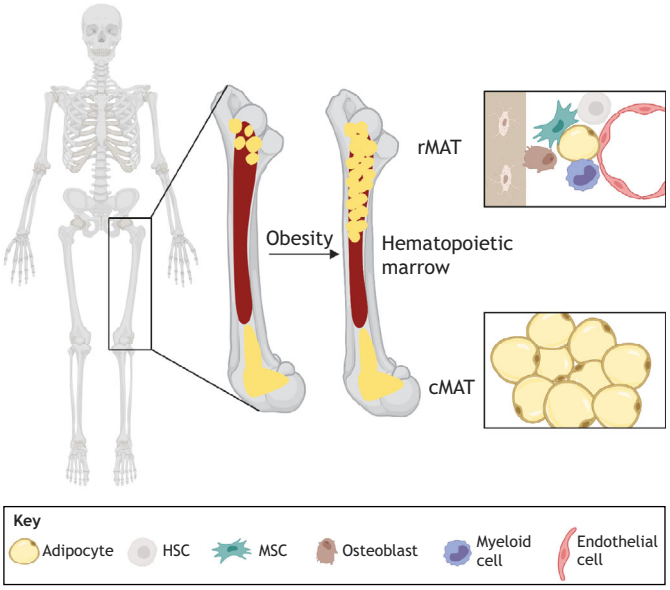

Fig. 1. Regional localization of bone marrow adipocytes. As depicted, bone marrow adipocytes may either be of the constitutive or the regulated marrow adipose tissue (cMAT and rMAT, respectively). Each bone has a proportionally higher abundance of one type over the other. Distal marrow sites are filled with cMAT, while proximal marrow regions contain rMAT. cMAT accumulate homogenously while rMAT accumulate intertwined with other cellular lineages. Therefore, rMAT are in constant communication with other cells to influence and be influenced in lineage determination decisions. Obesity increases the rMAT population, while cMAT is unchanged. HSC, hematopoietic stem cell; MSC, mesenchymal stem cell.

abundance of HSCs (Fig. 2) (Calvi et al., 2003; Weber and Calvi, 2010). Osteopontin, Wnt, N-cadherin, thrombopoietin and angiopoietin signaling have all been proposed to guide the above-mentioned osteoblast influence on HSCs (Adler et al., 2014b). Accordingly, a change in osteoblast number or function, as occurs with aging and chronic inflammatory disorders, likely exerts a marked influence on the balance of HSCs. Furthermore, osteoclasts, the bone-resorbing cells, cleave and thereby inactivate CXCL12 (Fig. 2) (Kollet et al., 2006). In states of obesity, where an increase in BMA occurs at a cost of osteoblasts, with a concomitant increase in osteoclasts, HSCs exponentially lose signals to maintain quiescence, which results in mobilization from the bone marrow niche.

Sinusoidal zone cell interactions

Moving centrally away from the inner bone marrow walls is the sinusoidal zone, where there is a gradual increase in ST-HSC abundance. In fact, the majority (~85%) of HSCs reside in this region (Cuminetti and Arranz, 2019). The sinusoidal zone gets its name from the many blood vessels present in this region that are lined with sinusoidal endothelial cells. Here, ST-HSC maintain hematopoiesis by proliferation for self-renewal and by differentiation into multipotent lineage-committed cells that replenish circulating blood cells (Ding et al., 2012). Bone marrow endothelial cells and leptin receptor-positive ($LepR^+$) perivascular cells express Kit ligand [KITLG, otherwise known as stem cell factor (SCF)], which has proven to be essential for HSC maintenance, although the exact mechanism is yet to be elucidated (Ding et al., 2012). $LepR^+$ perivascular cells and reticular cells also express CXCL12 (Fig. 2). The close proximity of the ST-HSCs to the vasculature allows for quick migration (Fig. 2) and transport of HSCs and their progeny in response to environmental cues that demand production of specific cell types. However, it also leaves these cells susceptible to chronic environmental changes that, over time, may skew HSC lineage determination.

HSCs are maintained and regulated by various signals and cell types in the surrounding microenvironment (Kato and Igarashi, 2019). These cell types include the vascular sinusoidal endothelial cells, perivascular stromal cells and mature hematopoietic cells. Among these cells, the vascular sinusoidal endothelial cells and perivascular stromal cells support the self-renewal of HSC by secreting CXCL12 and SCF, which play key roles in hematopoiesis (Kim et al., 2014). MSCs are a major source of CXCL12, which maintains HSCs within this niche. Conversely, mature hematopoietic cells are involved in HSC quiescence and localization through various pathways, including the transforming growth factor beta (TGF-β) and C-X-C motif ligand 4 (CXCL4) signaling pathways (Sarkaria et al., 2018). BMAs can also influence HSC regulation (Naveiras et al., 2009) and participate in hematopoietic regeneration, as discussed below (Zhou et al., 2017).

Hematopoiesis in the bone marrow

Hematopoiesis is the hierarchal differentiation processes by which all cellular components of the blood are formed from the LT-HSCs in the red bone marrow. The LT-HSCs are capable of both self-reconstitution and multipotency through sequentially generated populations, each more lineage-committed than the last (for a review, see Kato and Igarashi, 2019). Briefly, hematopoietic differentiation is divided into two principal streams, the myeloid and the lymphoid lineages, which constitute the innate and adaptive immune systems, respectively. The mature myeloid lineage cells, mediating the innate immune response, are erythrocytes, platelets, granulocytes, monocytes and macrophages. The mature lymphoid lineage cells, responsible for adaptive immunity, are B lymphocytes, T lymphocytes and natural killer cells – albeit with cellular maturation occurring in the lymph nodes and spleen (Marti et al., 2017). Innate immune cells are fast responders to a plethora of targets at a cost of specificity, whereas adaptive immune cells are highly target-specific at a cost of rapid action.

The LT-HSCs only make up 0.001% of all bone marrow cells (Challen et al., 2009). Instead, the predominant bone marrow hematopoietic component are hematopoietic progenitors at various states of maturity. Cells at all these various stages are vulnerable to changes in the soluble and cellular composition of the bone marrow (Kato and Igarashi, 2019). Thus, any changes that may affect intrinsic lineage-specific transcription factors, stochastic processes and extracellular signals in the bone marrow environment will influence proliferation, differentiation and lineage commitment of various cells (Teles et al., 2013; Zhu and Emerson, 2002). For example, the fate of LT-HSCs, ST-HSCs and their progeny can be influenced by hematopoietic cytokines, cell–cell interactions and metabolic changes in the bone marrow (Oburoglu et al., 2014). A disturbance in any of these components will impact the fate of HSCs and their lineage allocation.

An imbalance in favor of the myeloid lineage, as seen in chronic inflammatory disorders (Singer et al., 2014), results in tissue damage owing to the highly non-specific nature of the consequences of myeloid cell activation. Conversely, an imbalance in favor of the lymphoid lineage leads to lymphoproliferative disorders, such as in leukemia. Thus, it is critical to maintain hematopoietic homeostasis. Obesity, a multisystem disorder, is strongly associated with chronic inflammation and immunodeficiency leading to development of various metabolic imbalances as well as increased risk of infection

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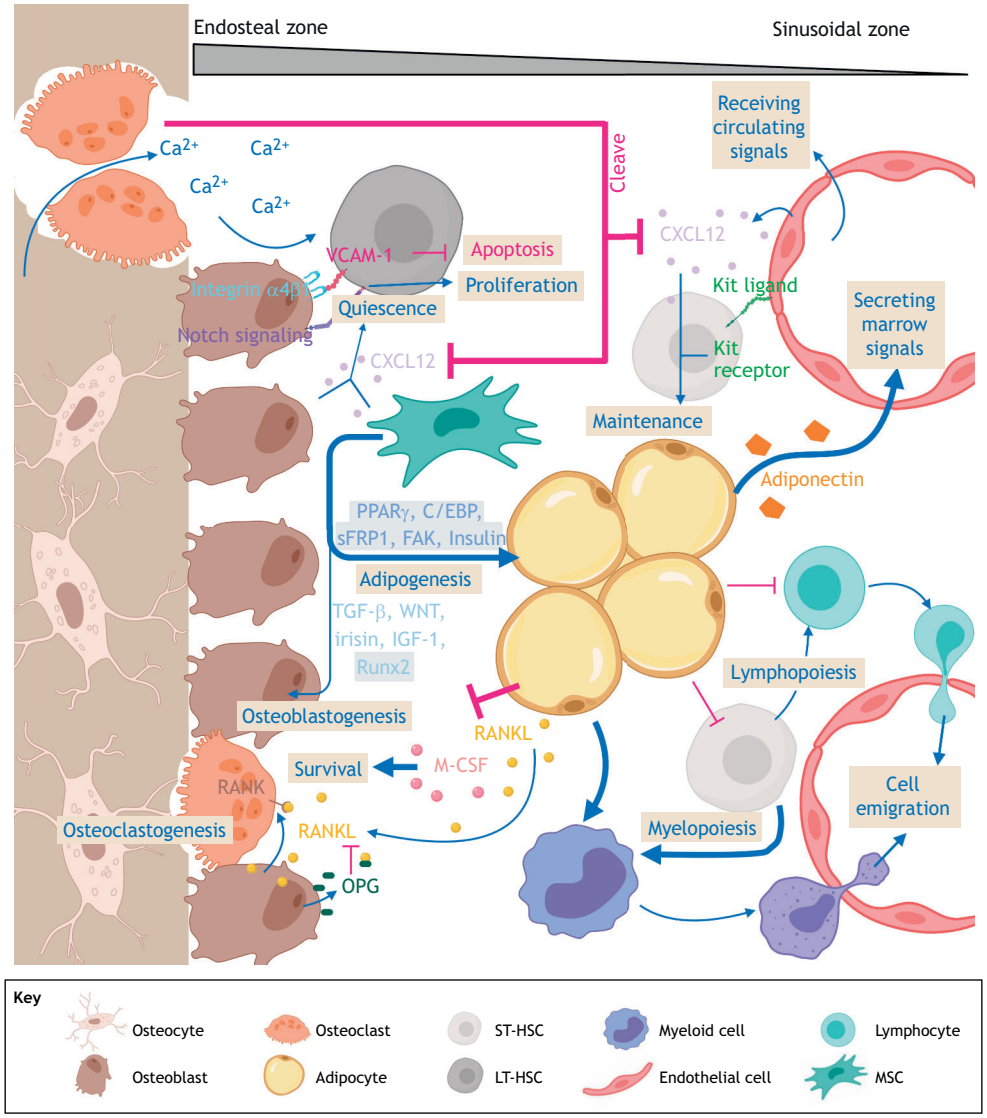

Fig. 2. Niches within the bone marrow determine cellular intercommunication and exposure to various micro-environments. In the endosteal zone of the bone marrow, a Ca^{2+} gradient drives LT-HSCs towards the outer endosteal zone, allowing for their interaction with osteoblasts and mesenchymal stem cells (MSC). These interactions are mediated by soluble factors CXCL12 and angiopoietin1, as well as by binding of vascular cell adhesion molecule 1 (VCAM-1) to integrin α4β1 and Notch receptor signaling. Collectively, LT-HSC are maintained in a quiescent state. MSC can reconstitute osteoblastic and adipogenic lineages through appropriate signals (see blue arrows and listed factors). Adipocyte expansion occurs at a cost to the osteoblastic and hematopoietic cellular lineages. In the inner sinusoidal zone of the bone, short-term (ST)-HSC give rise to the fully differentiated myeloid and lymphoid cells. Their unique localization allows for their bidirectional interaction with the endothelial cells of the arterioles and their emigration out of the bone marrow. Leptin receptor positive ($LepR^+$) endothelial cells of the endosteal arterioles can secrete CXCL12 and communicate through Kit receptor ligand signaling that allows for ST-HSC maintenance. The unique interaction and inter-communication of cellular components in these niches are vastly disrupted by physio-pathological challenges of obesity as indicated by bold arrows. Bone marrow adipocytes are key intermediates in many of these cellular interactions. Italicized text denotes which functional outcome is regulated. Shaded text denotes signaling pathways involved in lineage determination.

(Dixit, 2008; Karlsson and Beck, 2010). During states of obesity, hematopoietic lineage decisions are skewed towards myelopoiesis (Singer et al., 2014) and away from lymphocyte differentiation (Adler et al., 2014a,b) (Fig. 2). The increase in myeloid populations results in tissue infiltration of monocytes and their differentiation into pro-inflammatory macrophages that initiate tissue inflammation and exacerbate metabolic disease (Castoldi et al., 2016; Fink et al., 2014; Griffin et al., 2018). Mechanistically, high-fat-diet-induced obesity leads to a rapid suppression of bone marrow interleukin-7 (IL-7) (Adler et al., 2014a), which is an important factor in early lymphocyte development (ElKassar and Gress, 2010), thereby increasing susceptibility to infections and its associated mortality (Flegal et al., 2019). These skewed preferences are correlated with obesity-induced increases in BMAs, resulting in a change in bone marrow cellularity and a consequentially altered communication among cell types.

BMAs in lean and positive energy states

As with peripheral tissue adipocytes, BMAs expand to store excess energy in the form of triglycerides (see Table 1). Differences in the responsiveness between adipocytes of the yellow versus red marrow has given rise to the ‘dual BMA hypothesis’ (Craft et al., 2018). The differences were first identified by Tavassoli in response to phenylhydrazine-induced hemolysis in rabbits, where he described

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Table 1. Differences between adipocytes from peripheral tissue depots and the bone marrow

	Peripheral tissue adipocytes			Bone marrow adipocytes	
	White	Beige	Brown	Constitutive	Regulated
Localization	Subcutaneous Visceral (epididymal, mesenteric, epicardial) Ectopic	Interspersed in white or brown adipose depot and inducible upon stimuli	Interscapular Perirenal Cervical	Distal skeletal sites Homogeneous cellular niche Inaccessible to hematopoietic and other BM cells	Proximal, central and endosteal skeletal sites Complex multicellular niche allowing for cell–cell interactions
Cell morphology	Spherical Variable size (25 up to 200 µm)	Spherical Variable size	Elliptical Small (15–60 µm)	Spherical 'Larger' (37–41 µm)	Spherical 'Smaller' (30–36 µm)
Lipid droplet	Unilocular large lipid droplet Occupies most of the cytosol, organelles at periphery	Multilocular lipid droplet and additional lipid droplets Nucleus remains central	Multilocular and small lipid droplets	Unilocular (white-like) Accumulate myristoleic and palmitoleic acid	Unilocular (beige-like) Accumulate myristic and palmitic acid
Metabolic function	Store energy in the form of triglycerides	Store and burn fat for thermogenesis	Burn fat for thermogenesis	Stable: unaltered with physiological challenges	Labile: respond to environmental stimuli
Uncoupling protein 1 (brown adipocyte marker)	–	++	+++	–	+

fat cells of the yellow marrow as 'stable' while those in the red marrow as 'labile' (Tavassoli, 1976). Today, we understand that the yellow marrow is largely enriched in a population of adipocytes that are not responsive to environmental stressors and are therefore referred to as constitutive BMAs (cBMAs). Red marrow is largely comprised of adipocytes that are in a state of 'flow' as they can be expanded or depleted in response to endogenous and exogenous stimuli and are therefore referred to as regulated BMAs (rBMAs) (Fig. 1) (Scheller et al., 2015). Importantly, these allocations are loosely prescribed to clarify that the alternative adipocyte type in each marrow space is not completely absent (Craft et al., 2018).

Distal skeletal sites, which are filled with yellow bone marrow, contain cBMAs, which are larger in size, relatively resistant to lipid loss and remodeling, and store mono-unsaturated fatty acids, such as myristoleic and palmitoleic acid (Fig. 1) (Tavassoli, 1976). Marrow cellularity in these regions is homogenous, and hence adipocytes largely interact with other adipocytes (Craft et al., 2018). Conversely, the proximal, central and endosteal skeletal sites contain rBMAs, which are smaller in size, readily altered by environmental stimuli, maintain multicellular contact and accumulate saturated fatty acids, such as myristic and palmitic acid (see Table 1) (Craft et al., 2018; Tavassoli, 1976). These cells are interspersed amongst other cell lineages and therefore interact with a higher variety of cell types (Craft et al., 2018).

In lean states, BMAs are morphologically similar to bona fide white adipocytes as they contain a single fat globule. However, they also express the brown adipocyte markers, such as mitochondrial brown fat uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α (PGC-1α), PR domain-containing protein 16 (Prdm16), forkhead box protein C2 (FoxC2) and 3-adrenergic receptor, albeit in significantly less amounts than bona fide brown adipocytes (Krings et al., 2012; Sulston et al., 2016). However, brown adipocyte markers are reduced in obese mice and a parallel adoption of more white adipocyte markers is observed (Krings et al., 2012). Additionally, rBMAs expands both in cell size (hypertrophy) and cell number (hyperplasia) through activation of PPARγ during obesity (Rosen and MacDougald, 2006). The culmination of the upregulation of white adipocyte proteins as well as the increase in fat storage capacity leads to bone marrow adipocyte whitening. The direct mechanistic consequences of adipocyte whitening on hematopoietic lineage development have not been investigated. However, given the vastly different metabolic and soluble factors between bona fide white and brown adipocytes, it is easy to imagine that a skewing in adipocytes to either type (white or brown) will vastly alter the marrow microenvironment and the factors that surround hematopoietic cells.

Given the fixed space within the bone marrow cavity, the expansion of MAT leaves less space for hematopoietic and other cellular lineages. Therefore, the bone marrow niche is vastly remodeled not only through changes in lineage development and space availability for other cell niches, but it also poses a physical barrier challenging cell migration within the cavity space. This may reduce cell–cell interactions by affecting cellular traffic. Impaired cell migration has implications for bone formation and bone disease (Su et al., 2018) as well as for lymphocyte maturation processes (Tokoyoda et al., 2004). Enhancing MSC migration has been proposed as a promising strategy for reversing bone loss and bone disorders (Su et al., 2018). Cell migration within the marrow cavity is also necessary for B cell development to an area of chemokine CXCL12-secreting cells followed by migration to another niche with IL-7^+ cells (Tokoyoda et al., 2004). Therefore, the physical constraint from the expansion of MAT would be manifested by restricted migration of MSC and B cells, hindering bone and lymphocyte maturation.

The bone marrow adipose depot as an endocrine organ

Visceral and subcutaneous adipose tissue depots are recognized as endocrine organs made up of adipocytes and hematopoietic cells that interact with each other and contribute significantly to body metabolism (Ferrante, 2013; Kershaw and Flier, 2004). Likewise, MAT has recently been recognized as an endocrine organ contributing to local and systemic adiponectin and leptin production (Cawthorn et al., 2015; Sulston and Cawthorn, 2016). Increased local leptin – as seen in obesity – that is released from MAT can stimulate MSCs through the LepR to skew their differentiation in favor of adipogenesis. In this way, increased

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leptin secretion from MAT creates a positive feedback loop that amplifies bone marrow adiposity and perpetuates hematopoietic abnormalities (Yue et al., 2016). This novel discovery is the first evidence that bone marrow adipocytes are not only space fillers, rather they are important cellular components, not only for the bone marrow niches but also for whole-body effects.

Changes in the levels of adipocyte factors are transmitted to the circulation through endosteal arterioles (Fig. 2). The marrow vascularization allows for continuous bidirectional communication with the rest of the body, receiving 10% of total cardiac output (Riddle and Clemens, 2017). Interestingly, the exchange of factors is still tightly controlled in order to create a unique micro-environment that is different from the circulation. This was highlighted by the discovery that the marrow lipid composition, while still amenable to reception of circulatory stimuli, is distinct from that found in serum (Miranda et al., 2016). The role of lipids in the bone marrow were recently highlighted in an excellent review (Rendina-ruedy and Rosen, 2019).

MSC fate in the bone marrow

MSCs, the 'other' stem cells of the bone marrow, are also self-renewing and tripotent, giving rise to osteoblasts, chondrocytes and adipocytes. Mesenchymal lineage decisions have been linked to the preference in signal transduction of PPARγ, CCAAT/enhancer-binding protein (CEBP) and secreted frizzled-related protein 1 (sFRP1) signaling pathways for adipogenesis, and WNT, TGF-β, irisin, runt-related transcription factor 2 (Runx2) and insulin-like growth factor 1 (IGF-1) signaling pathways for osteogenesis (Fig. 2), respectively (Li et al., 2018; Tencerova et al., 2018). Obesity enhances the proliferative capacity of MSCs and skews their differentiation in favor of the adipocyte lineage by downregulation of Runx2 and upregulation of adipogenesis markers CEBP-α, PPARγ and therefore the gene expression of adiponectin, an early adipogenic gene transcriptionally regulated by PPARγ (Bouskila et al., 2005; Fain et al., 2008). Da Silva et al. showed that upregulation of PPARγ is due to obesity-induced increases in tumor necrosis factor (TNF) largely contributed by HSCs (da Silva et al., 2016). Obesity also leads to elevation of pro-inflammatory cytokines IL-1β and IL-6 in the bone marrow (Halade et al., 2011). Therefore, obesity creates a pro-inflammatory environment within the bone marrow mediated by HSCs that feed back onto MSCs and shift their lineage outcome towards adipogenesis (Fig. 2).

The transcriptional landscape and intracellular signaling cascades responsible for bone marrow MSC adipocyte lineage commitment and maturation have been further identified in humans (Ali et al., 2018). Interestingly, focal adhesion kinase (FAK, also known as PTK2) and insulin signaling were the most upregulated pathways. FAK signaling is also required for adipocyte survival, expansion and their insulin sensitivity (Luk et al., 2017). The insulin response of BMA was nicely reviewed recently (Tencerova et al., 2019) and will not be further elaborated upon here.

Given the varied results in identifying a common adipogenic stem cell, it has been hypothesized that the origin of BMAs may be heterogeneous and that they may derive from different progenitor cells in the bone marrow (Li et al., 2018). This model is supported by the spatial localization of MAT within the bone cavity and across the skeleton (Fig. 1) as well as by the varied responsiveness of MAT to environmental stressors (Scheller et al., 2015). However, other groups have provided evidence that a single population of MSCs, defined as CXCL12 abundant reticular (CAR)/LepR^{+}/Nestin-GFPdim cells, are plentiful in various bone marrow niches (Zhou et al., 2014) and are an important contributor to adipocyte cellularity and communication with HSCs (Omatsu et al., 2010; Sugiyama et al., 2006). This is supported by the finding that BMAs are vastly depleted when the adipo-osteogenic progenitor-specific transcription factor FoxC1 is absent in CAR/LepR^{+} MSCs (Omatsu et al., 2014). These discrepancies in identifying BMA precursors may be due to the diverse markers used in classifying MSCs (Box 1).

Like HSCs, lineage skewing of a multipotent stem cell comes at a cost to its other lineage branches. The obesity-induced increase in MSC differentiation in favor of adipogenesis is therefore at a cost to the osteoblastic lineage population (Keats et al., 2014). A body mass index of more than 30 is strongly associated with elevated expression of the ER-stress-related proteins activating transcription factor 4 (ATF4) and CEBP-homologous protein (CHOP, also known as DDIT3) in MSCs, resulting in reduced MSC differentiation, proliferation and increased senescence (Ulum et al., 2018). Importantly, MSCd and their osteoblastic progenitors communicate with HSCd by secreting CXCL12 to home HSCs to niches within the bone marrow (Méndez-Ferrer et al., 2010). Osteoblasts regulate osteoclast populations through inhibitory osteoprotegerin (OPG, also known as TNFRSF11B) signals, which antagonize the action of the receptor activator of nuclear factor κB (RANK) ligand (RANKL, also known as TNFSF11) released by pre-adipocytes (Halade et al., 2011). During obesity, secreted cytokines from adipocytes and preadipocytes, such as adiponectin, RANKL and SCF, are increased to promote osteoclastogenesis and myelopoiesis (Takeshita et al., 2014). Therefore, the obesity-induced upregulation of osteoclast-specific cathepsin k and RANKL, concomitant to the downregulation of osteoblast-specific Runx2 and along with decreases in OPG, create an imbalance towards bone resorption (Halade et al., 2011), which exacerbates Ca^{2+} release and LT-HSC recruitment (Fig. 2) (Adams et al., 2006). Additionally, adiponectin, released by adipocytes, has opposite effects on lymphoid and myeloid lineages by, concomitantly, reducing B lymphopoiesis and enhancing myelopoiesis through prostaglandin synthesis (Bilwani and Knight, 2012; Yokota et al., 2003). Thus, an imbalance in MSCs will be sensed by the HSCs (Fig. 2). The regional proximity of MSCs and HSCs allows for their bidirectional communication in normal and obese states. The HSCs convey inflammation to MSCs to influence pro-adipogenic lineage determination with obesity, and MSCs

Box 1. Refined identification markers for bone marrow MSCs

MSCs were originally identified as plastic-adherent cells that test positive for CD73, CD90 and CD105, and negative for CD34, CD45, CD14 or CD11b, CD79a or CD19, and human leukocyte antigen – DR isotype (HLA-DR) – surface markers (Dominici et al., 2006). However, this suite of markers has since proven controversial or insufficient and many groups have further worked to refine the identification system. Cells negative for CD45 and CD31 but positive for stem cell antigen-1 (Sca1) and CD24 were later classified to give rise to the osteochondrogenic progenitor cells, which are negative for CD45, CD31 and Sca1 and positive for platelet-derived growth factor receptor α (PDGFRα). They were also shown to give rise to adipogenic lineage-committed cells, which are negative for CD45, CD31 and CD24, and positive for Sca1 (Ambrosi et al., 2017). The adipogenic-lineage-committed cells were shown to differentiate to pre-adipocytes, which are negative for CD45, CD31 and Sca1, but positive for zinc finger protein 423 (zfp423) (Ambrosi et al., 2017). Furthermore, several other markers such as osterix (Osx), leptin receptor (LepR), nestin (Nes) and Gremlin1 (Grem1) have also proven reliable to classify bone marrow MSCs (Mohamed et al., 2017).

directly and indirectly home and maintain senescence of HSCs, which is disrupted in obese states (Fig. 2).

MAT is a unique adipose tissue source

Whereas peripheral adipose tissue is a good model to understand the dynamics of MAT, peripheral tissue adipocytes and BMAs differ in many ways (see Table 1). First, the proportion and abundance of adipocytes to hematopoietic cell lineage cells is vastly different in each organ. Second, the BMA reside in a spatially fixed compartment; thus, their expansion may be at a cost to other cells, as discussed above. Third, BMAs are in close contact to cells that peripheral adipocytes are not exposed to such as bone, stromal and various stem and precursor cells. Finally, BMAs do not display catabolic response to β-adrenergic receptor stimulation and thus very little lipid mobilization from BMAs occurs (Scheller et al., 2019), unlike the dynamic lipid uptake and lipolysis of peripheral adipocytes. Etiologically, lineage-tracing studies have revealed that MAT does not share precursors with either white or brown peripheral adipocytes (Scheller et al., 2015). Interestingly, an extracellular glycoprotein called tenascin, identified as a link between inflammation and extracellular remodeling, is upregulated in the stromal vascular fraction of visceral white adipose tissue (Catalán et al., 2012) and is also elevated in the bone marrow MSCs during obesity (da Silva et al., 2016). This indicates that the obesity-induced changes in visceral and marrow adipocytes (i.e. adipocyte expansion, whitening, and communication with inflammatory signals) are similar in both loci. Therefore, in studying MAT, comparisons with visceral adipocytes may be made while being cognizant of the fact that MAT is a unique adipose tissue depot. Hence, although the interplay of adipocytes and immunological cells in peripheral tissue serves as a good rationale to understand their communication in the bone marrow, there are developmental, contextual and functional features defining each depot, such that MAT can genuinely be considered a singular type of adipose tissue.

Conclusions and perspectives

BMAs are no longer thought of as mere space fillers of the bone marrow. They are now recognized as heterogeneous cells that make up a distinct adipose depot in the bone marrow capable of influencing cellular decision making, and these naturally contribute to changes in whole-body circulating factors. BMAs resemble peripheral adipocytes in many ways; however, there are distinct differences, which may be due to their unique function, nature and localization (Table 1). Therefore, although bona fide peripheral adipocytes may be good models for extrapolating properties of BMAs, further advancements in BMA isolation techniques are required to fully understand their function and interaction with other cellular lineages.

The bone marrow is home to a diversity of cell types that interact with each other through cell–cell contact, secreted factors and their physicochemical gradients through the formation of various niches. Although, in obesity, BMA characteristics shift from brown and/or beige-like adipocytes to white adipocytes, it is unknown whether this shift occurs due to conversion of brown adipocytes, whitening of beige adipocytes or expansion of the white adipocyte lineage. Future lineage tracing studies should focus on addressing this question to better understand ways in which we may prevent BMA whitening and expansion. This will also allow us to understand how imbalances in cellular, physical and chemical factors impacting on BMAs can lead to disruption of hematopoietic quiescence, proliferation and preferential differentiation, contributing to the low-grade inflammation that has come to characterize obesity and type 2 diabetes.

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Competing interests

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