HHS Public Access

Author manuscript

Cytometry A. Author manuscript; available in PMC 2018 July 31.

Published in final edited form as:

Cytometry A. 2018 February ; 93(2): 167–171. doi:10.1002/cyto.a.23301.

Adipocytes role in the bone marrow niche

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Abstract

Adipocyte infiltration in the bone marrow follows chemotherapy or irradiation. Previous studies indicate that bone marrow fat cells inhibit hematopoietic stem cell function. Recently, *Zhou et al.* (2017) by using state-of-the-art techniques, including sophisticated Cre/loxP technologies, confocal microscopy, *in vivo* lineage-tracing, flow cytometry, and bone marrow transplantation, reveal that adipocytes promote hematopoietic recovery after irradiation. This study challenges the current view of adipocytes as negative regulators of the hematopoietic stem cells niche, and reopens the discussion about adipocytes' roles in the bone marrow. Strikingly, genetic deletion of stem cell factor specifically from adipocytes leads to deficiency in hematopoietic stem cells, and reduces animal survival after myeloablation, The emerging knowledge from this research will be important for the treatment of multiple hematologic disorders.

Keywords

adipocytes; hematopoiesis; hematopoietic stem cells; bone marrow

Owing to the modern sedentary lifestyle, excessive fat accumulation in the body has become a worldwide epidemic, leading to immense research interest on the pathophysiological role of adipose tissue in several diseases (1,2). Fat stores energy and maintain body temperature in response to cold by generating heat (3). Furthermore, adipose tissue may act as an endocrine organ, producing an enormous repertoire of biologically active molecules, placing fat cells as key determinants for healthy metabolism and in multiple dysfunctions (4,5). Lately, our knowledge on adipose tissue biology has rapidly progressed, associating fat cells with sometimes unexpected roles throughout the organism.

Fat tissue is highly heterogeneous among distinct anatomical depots, differing in its physiological and pathological roles (6). In the bone marrow, adipocytes are smaller and

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DISCLOSURES

The authors indicate no potential conflicts of interest.

appear dispersed, instead of being grouped into lobules as subcutaneous and visceral fat cells (7). Although the presence of bone marrow adipocytes histologically was detected long time ago, they have been erroneously ignored in the past, and considered merely inert cells “space fillers”. Curiously, physicians even denominate as hypocellular the adipocyte-rich bone marrow biopsy. Thus, until recently the functions of fat cells in the bone marrow were poorly explored. Only recently, growing evidence show that bone marrow adipose tissue affects insulin metabolism, energy expenditure, and bone mass (8). Fat cells secrete fatty acids, hormones, adipokines, and cytokines, which may have profound effects on the function of other neighboring cell populations in the bone marrow microenvironment (9,10).

The most illustrious residents of the bone marrow are the hematopoietic stem cells which give rise to all blood and immune cells throughout life, including platelets (11), erythrocytes, and white blood cells (12). Without hematopoietic stem cells, we would not be capable to preserve blood cell counts and would die shortly due to bleeding (as a result of platelet reduction), anemia (as a result of erythrocytes depletion), and infection (as a result of immune cells deficiency) (7). Adipocytes increase in the bone marrow microenvironment with aging, and after chemotherapy or irradiation (13). Hence, numerous studies have been carried out to explore how fat cells affect hematopoietic stem cells in the bone marrow (14–18). These works indicate that bone marrow fat cells inhibit hematopoietic stem cell function, repressing their growth and differentiation (14). However, in a recent article in Nature Cell Biology, Zhou and colleagues challenge the current view of adipocytes as negative regulators of the hematopoietic stem cells niche in the bone marrow (19). The authors demonstrated that fat cells promote increased hematopoiesis in response to myeloablation (19) (Figure 1). Zhou and colleagues investigated the role of bone marrow adipocytes as hematopoietic stem cell niche components by using state-of-the-art techniques, including sophisticated Cre/loxP technologies, confocal microscopy, *in vivo* lineage-tracing, and bone marrow transplantation. These experiments revealed that bone marrow fat cells from irradiated and non-irradiated mice produce high amount of stem cell factor, an essential cytokine that plays a pivotal role in hematopoietic stem cell maintenance. Strikingly, genetic deletion of stem cell factor specifically from adipocytes inhibited hematopoietic regeneration after myeloablation, leading to deficiency in hematopoietic stem cells, and reducing animal survival. Interestingly, genetic deletion of the same cytokine from other important cells present in the niche (osteoblasts, endothelial or hematopoietic cells) did not affect hematopoietic recovery after 5-fluorouracil treatment or irradiation. Additionally, Zhou and colleagues showed that in the caudal vertebrae, where adipocytes are more abundant, hematopoietic stem cell maintenance depends on stem cell factor produced in fat cells.

Here, we discuss the findings from this work, and evaluate recent advances in our understanding of adipocyte contribution to the hematopoietic stem cell niche.

PERSPECTIVES / FUTURE DIRECTIONS

The use of traditional transgenic knockout mice models has proved to be beneficial for the discovery of the role of key molecules in physiological and pathological states. Nevertheless, these technologies produce broad changes in gene function throughout the body, affecting

several tissues and cell types. Thus, they are limited in that they do little to identify the specific roles of a protein in a specific cell type from a specific tissue in a concrete moment (20). Because the molecular functions of genes may depend on a specific subset of cells in which they are expressed, restricting gene manipulation to specific cells in the organism may be useful to understand protein functions in different cell populations (21). Thus, conditional gene manipulation strategies offer a powerful tool. The main findings from this study are based on the data obtained from tamoxifen-inducible Adipoq promoter driven CreER-LoxP system (22). Adipoq encodes adiponectin, an adipokine expressed in fat cells (23). Note however that expression of Adipoq is not restricted to adipocytes. Bone-forming cells, cardiomyocytes, and skeletal muscle fibers also may express Adipoq under specific pathophysiological conditions (24–26). Additionally, in Adipoq-CreER mice, recombinase expression is not limited adipocyes in the bone marrow, as adipocytes from fat depots in other organs are marked as well. Thus, in Adipoq-CreER/stem cell factor floxed mice, stem cell factor deletion is not restricted to bone marrow adipocytes. Future studies should evaluate the contribution of other possible sources from outside the bone marrow to hematopoiesis.

The hematopoietic stem cells niche in the bone marrow that supports the homeostasis of those cells is a complex microenvironment composed, besides adipocytes, of osteoblasts, osteocytes, osteoclasts, endothelial cells, smooth muscle cells, pericytes, fibroblasts, macrophages, megakaryocytes, lymphocytes, hematopoietic progenitors, neutrophils, peripheral innervations, and Schwann cells (7,27–37). Although recent studies have revealed the contributions of distinct components of the bone marrow to hematopoietic stem cells regulation, little is known about the cross-talk between these cellular components. Future studies should explore how adipocytes affect and are affected by other hematopoietic stem cell niche constituents. Interestingly, a recent study revealed that sympathetic nerves in the bone marrow are critical for efficient hematopoietic recovery after 5-fluorouracil treatment or irradiation. Further studies will be needed to explore in depth which bone marrow cells are targeted by the sympathetic nervous system. The relationship between sympathetic nerves and adipocytes in hematopoietic recovery after genotoxic insults will need to be explored in great detail.

During development, murine hematopoiesis takes place at specific anatomical locations (12). It begins at embryonic day 7.5 in the extraembryonic yolk sac; at embryonic day 9, it progresses in the para-aortic splanchnopleura, chorioallantoic placenta (38), and aorta–gonad–mesonephros; and at embryonic day 10 it happens in the fetal liver, where a huge expansion of hematopoietic stem cells occurs. Finally, at embryonic day 15, it starts in the bone marrow, where it stably occurs throughout the whole adult life (39). Hematopoiesis can also develop under special pathological circumstances external to the bone marrow medullary spaces. Extramedullary hematopoiesis was reported in adults in the adrenal glands, periosteum, heart, spleen, liver, fatty tissue, pleural cavity, kidney, pre-sacral region, intra-spinal tissue, para-vertebral regions, nasopharyngeal region, para-nasal sinuses, and several types of benign and malign cancers (40–45). It remains to be elucidated whether adipocytes provide and adaptive niche, serving hematopoiesis at multiple developmental stages of mammalian life, or only in the bone marrow. Also, it will be interesting to explore the role of adipocytes as a niche cell in extramedullary hematopoiesis.

Zhou and colleagues revealed that adipocyte derived-stem cell factor is important for hematopoiesis (19). Stem cell factor is expressed by a number of bone marrow cell types as several other cytokines that bind to receptors on hematopoietic stem cells. The complex regulation of the multiple fates of hematopoietic stem cells, including self-renewal, quiescence, differentiation, and mobilization from the bone marrow niche, requires the cooperative orchestration of several cytokines. Future studies should explore whether other adipocyte-derived signals may be as important as stem cell factor for hematopoiesis. Multiple molecules important in hematopoietic stem cell regulation were identified, including stromal cell derived factor (CXCL12 chemokine) (46), bone morphogenic proteins (47), transforming growth factor β (48), Thrombopoietin (49), the Notch ligands Delta and Jagged (50), Angiopoietin-1 (51), Angiopoietin-like proteins (52), Insulin-like growth factor 2 (53), fibroblast growth factors (FGF) (54), VCAM-1 (55), Wnt signaling ligands (56), interleukin-10 (57), and others (58,59). Future studies will reveal whether those molecules are important in adipocytes-regulation of bone marrow hematopoiesis.

Knowledge about how hematopoietic stem cell are regulated in their normal bone marrow microenvironment has led to progress in the characterization and understanding of how leukemic stem cells interact with their niche. Recent studies have shown that alterations in the normal bone marrow microenvironment may trigger the formation of pre-leukemic niches (60). Recent studies suggest active participation of resident adipocytes in tumor biology (61–63). This growing evidence highlight the need for further investigation of the adipocyte derived signals involved in the bone marrow fat tissue influence on leukemia cell survival, progression, and spread. While Zhou and colleagues reveal that adipocyte-derived stem cell factor is an essential factor for hematopoietic stem cell regulation (19), its role in the modulation of tumor burden still needs to be explored. The mechanistic understanding of leukemic stem cells protection, through modulation of local concentrations of chemotherapy, support of tumor cells in a dormant state, or stimulation of overt anti-apoptotic signaling cascades is essential to the development of novel therapeutic strategies to blunt residual disease. Whether bone marrow adipocytes-derived signals are important in these processes, and specifically the stem cell factor, remains unknown.

Hematopoietic stem cells change functionally with physiological age (64). The alterations noted in aged hematopoietic stem cells were until recently thought to be a consequence of cell-intrinsic modifications (65,66). Nevertheless, new data the important role of multiple extrinsic factors in driving hematopoietic stem cell aging (67). Zhou and colleagues investigated the importance of adipocyte-derived stem cell factor in genotoxic insults in the bone marrow (19). It will be interesting to explore the role of adipocyte-derived stem cell factor on hematopoietic stem cells during bone marrow aging.

Hematopoietic stem cells represent a heterogeneous cell population based on their molecular markers (7), life span (68), differentiation capabilities (69), and degree of self-renewal (70). Little is known about the extrinsic regulation of hematopoietic stem cell subpopulations. The functional heterogeneity of hematopoietic stem cells points to the potential for matching heterogeneity in the niche influences that support the function of hematopoietic stem cell subsets. For instance, it is unclear whether adipocyte-derived stem cell factor affect differently distinct hematopoietic stem cell subpopulations. The anatomy of the bone

marrow is complex, and the heterogeneity within bone marrow adipocytes was not explored yet. Are all adipocytes in the bone marrow equal? If not, is there a specific adipocyte subgroup more important for hematopoiesis regulation? The genetically modified mice and imaging technologies allow us to follow specific cells at a single level (71,72). These powerful tools help us to elucidate the exact roles of particular cell populations in several functions (73–78). These techniques will further reveal the complex nature of the mechanisms by which extrinsic factors regulate signal transduction and cell-fate decisions of hematopoietic stem cells. In addition to studies in genetic mouse models, transcriptomic and single cell analysis after fluorescence activated cell sorting of live cells represent fundamental tools that will help us understand the roles of adipocytes within the bone marrow microenvironment (79–82). In spite of powerful experimental mouse models providing a proof of concept for adipocytes biology in the bone marrow, we are still lacking direct demonstration of adipocytes roles in the human bone marrow. The main challenge for the future will be to translate mouse research into humans. Improving the availability of human tissue samples will be essential to reach this goal. The isolation of adipocytes by cytometry from human bone marrow biopsies may support the data provided by elegant mouse model studies.

In conclusion, the study by Zhou and colleagues reveal a novel important role of adipocytes in hematopoietic stem cells regulation in the bone marrow, adding knowledge to the progress being made in elucidating the key cells responsible for regulating the hematopoietic niche. Transgenic mouse models, powerful imaging techniques, cell sorting, and single cell gene analysis have led to a more comprehensive understanding of hematopoietic stem cell niche cellular components. Although these technological improvements have clarified certain longstanding questions, our understanding of the exact origin, identity and detailed function of the majority of bone marrow cells remained to be studied in greater detail. Thus, our understanding of hematopoietic stem cells regulation in their niche still remains limited, and the complexity and interactions of different cellular components of the bone marrow microenvironment in diverse pathophysiological conditions should be elucidated in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Alexander Birbrair is supported by a grant from Pró-reitoria de Pesquisa/Universidade Federal de Minas Gerais (PRPq/UFMG) (Edital 05/2016); Akiva Mintz is supported by the National Institute of Health (1R01CA179072-01A1) and by the American Cancer Society Mentored Research Scholar grant (124443-MRSG-13-121-01-CDD).

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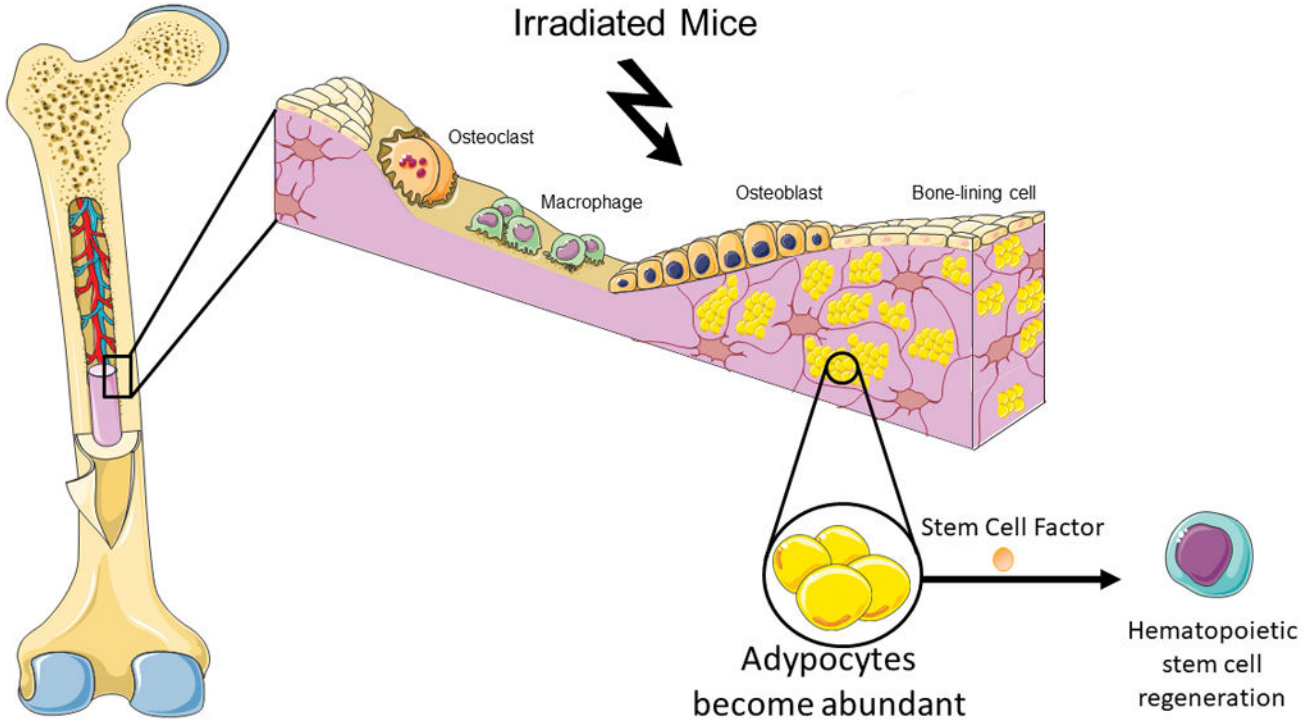

Figure 1. Adipocytes promotes hematopoietic regeneration in the bone marrow

Adipocytes increase in the bone marrow microenvironment with after irradiation. The study of Zhou and colleagues now reveals a novel very important function for adipocytes in the hematopoietic stem cells recovery after myeloablation (19). Adipocyte-derived stem cell factor mediate hematopoietic regeneration in the bone marrow, and absence of stem cell factor specifically in adipocytes leads to deficiency in hematopoietic stem cells, and reduces animal survival.

Future studies will reveal other roles of adipocytes in the bone marrow niche, and whether a specific hematopoietic stem cell subpopulation is regulated by adipocytes.