Current Molecular Biology Reports (2018) 4:117–122
https://doi.org/10.1007/s40610-018-0098-6

MOLECULAR BIOLOGY OF BONE MARROW FAT ADIPOSITY (B VAN DER EERDEN, SECTION EDITOR)

Bone Marrow "Yellow" and "Red" Adipocytes": Good or Bad Cells?

Domenico Mattiucci[1] · Olaia Naveiras[2] · Antonella Poloni[1]

Published online: 9 August 2018

Abstract

Purpose of Review Replacement of red hematopoietic bone marrow with yellow adipocyte-rich marrow constitutes a physiological process associated with aging. Adipocytes have recently emerged as an active part of the bone marrow niche and exert paracrine and endocrine functions, thereby contributing to the regulation of hematopoiesis. Here, we review the current understanding of the interactions between bone marrow adipocytes (BMAs) and hematopoietic cells, as well as their potential role in the progression of hematological malignancies.

Recent Findings Until recently, BMAs have been considered space-filler cells. Emerging evidence, however, associates BMA abundance with hematopoietic regulation. On the one hand, human clinical data and experimental findings from animal models suggest that BMAs may act as negative regulators of the hematopoietic microenvironment. On the other hand, recent data has also shown BMAs to exert positive effects on hematopoietic stem cell (HSC) survival. These seemingly contradictory effects could be explained either by a differential effect of distinct BMA subtypes on hematopoiesis, or by a differential response to BMA stimulation in HSCs versus their committed progeny. Two distinct types of bone marrow adipocytes have previously been described based on anatomical localization. Adipocytes located in the "yellow" marrow are bigger in size, less responsive to environmental stimuli, and associated with HSC quiescence. On the contrary, adipocytes situated within regions of hematopoietically active "red" marrow are significantly more labile and provide important support to regenerating blood populations. Moreover, beyond the presumed differential role of BMA subtypes in hematopoiesis, an imbalanced proportion of stromal constituents could impair their capacity to provide a protective role. Indeed, if BMA commitment has been shown essential for hematopoietic regeneration, skeletal regions constitutively enriched in BMA would be poorly vascularized, which would in turn negatively affect HSC support. Recently, the interplay of adipocytes and solid cancer has been revealed, with adipocytes promoting the growth of breast, ovarian and prostate cancers. BMAs have been no exception, playing an active role in the support of neoplastic cells in the bone marrow niche, particularly for bone metastatic disease and acute lymphoblastic leukemia (ALL). Acute myeloid leukemia (AML), however, actively suppresses BMAs, which results in impaired myelo-erythroid maturation.

Summary It is becoming increasingly evident that BMAs are ideally placed to interact with normal and malignant hematopoiesis. As such, elucidating the relationship between BMAs and specific hematopoietic cell types represents a novel avenue to explore therapeutic strategies for the treatment of hematological malignancies.

This article is part of the Topical Collection on *Molecular Biology of Bone Marrow Fat Adiposity*

✉ Antonella Poloni
a.poloni@univpm.it

[1] Clinica di Ematologia, Dipartimento Scienze Cliniche e Molecolari, Università Politecnica Marche, Via Tronto 10, 60126 Ancona, Italy

[2] Laboratory of Regenerative Hematopoiesis, School of Life Sciences, Swiss Experimental Cancer Research Institute (ISREC) and Institute of Bioengineering (IBI), École Polytechnique Fédérale de Lausanne (EPFL) & Hematology Division, Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Keywords Bone marrow adipocytes · Hematopoiesis · Microenvironment · Hematopoietic stem cells · Mesenchymal stromal cells · Leukemia

Introduction

The bone marrow (BM) represents the main hematopoietic organ in adults, as its microenvironment contains a variety of cell types at different maturation stages and is responsible for the lifelong production of mature blood cells. Along with hematopoietic elements, the BM microenvironment includes stromal constituents such as adipocytes (BMA), osteoblasts, and skeletal stromal cells (SSCs), which all play an active role in regulating hematopoiesis through cell-cell contact and the secretion of growth factors and cytokines.

BM-As are the most abundant stromal component found in the BM niche. They progressively increase with aging, physiologically replacing the hematopoietic components, and eventually occupying up to 70% of the medullary cavity of long bones. BMAs were historically considered insignificant, space-filling cells until a few years ago, but emerging evidence has linked the presence of these cells to the regulation of the hematopoietic microenvironment [1, 2]. Human clinical data and experimental findings from animal models suggest that BMA may act as negative regulators of the BM microenvironment affecting hematopoiesis and bone regeneration [3, 4, 5••]. However, recent in vitro findings also demonstrated that these cells may exert a positive role in the support of hematopoietic stem cells (HSC) survival by expressing MSC markers and as a source of cytokines and adipokines [6•, 7–11, 12••, 13].

BMAs are morphologically similar to adipose tissue adipocytes, as they present a single, large cytoplasmic lipid droplet that accounts for approximately 90% of the cellular volume and they originate from mesenchymal-like progenitor cell [14, 15]. The ability of both cellular populations to accumulate and release fatty acids might suggest that BMAs could contribute to energy balance. However, it has been long noted that BMAs paradoxically increase upon malnourishment and hibernation and that, contrarily to the peripheral white fat depots, which include subcutaneous and visceral fat, BMA are resistant to starvation-induced lipid mobilization [16, 17]. Furthermore, Cawthorn and colleagues have recently demonstrated that BMAT mass increases during controlled, moderate (30%) caloric restriction (CR), quantitatively demonstrating the inverse relationship between body mass index and marrow adiposity. The authors could further show that BMAs constitute an important source of circulating adiponectin in CR, a phenomenon blunted in Ost-Wnt10b−/− mice which have a defect in marrow adipocyte production [18]. These findings dismiss the idea that BMAs act as caloric reservoir, apart from in extreme CR conditions, and suggest that BMAs likely play different roles in the maintenance of energy homeostasis [19–21].

Noteworthy, it has been demonstrated that lipolysis of BMA may be induced by neoplastic cells, which employ fatty acids as an energy source to promote their survival and proliferation. In acute myeloid leukemia (AML), neoplastic cells are able to modify BMA metabolism to activate lipolysis and enable the transfer of fatty acids from adipocytes to AML blasts [22]. This has also been shown to orchestrate T-acute lymphoblastic leukemia blast propagation, demonstrating that AML impairs the BM adipocyte niche preventing continued maturation of healthy myeloid and erythroid cells [23••].

Bone Marrow Adipocytes and Hematopoiesis

HSCs are small, quiescent cells that reside within a highly regulated BM niche. They harbor self-renewal and differentiation capabilities, and are responsible for the production of mature blood elements throughout a human lifetime.

The importance of the BM niche as a highly organized microenvironment was first supported by Schofield in 1978 [24]. This specialized microenvironment provides structural and trophic support through its stromal components for HSC survival and proliferation. BMA, one of the major stromal components, therefore may play a significant role in the regulation of the hematopoietic niche.

In 1976, Tavassoli first proposed a distinction between two BMA populations, based on differences in lipid profiles and in histology with performic acid-Schiff staining (PFAS). PFAS-positive BMAs are widely dispersed throughout the hematopoietic tissue and disappear with hematopoietic expansion, while non-stained adipocytes accumulate regionally and remain unaffected by changes in hematopoiesis [25].

Recently, this model has been reconsidered, as newfound evidence demonstrates that the role and features of BMA subtypes may vary depending on their anatomical localization. It has been demonstrated that BMA in the distal skeleton are bigger in size, have an increased proportion of monounsaturated fatty acids, and are less responsive to environmental stimuli. These adipocytes have been described as part of the constitutive marrow adipose tissue (cBMAT) and seem to be different from the regulated marrow adipose tissue (rBMAT) adipocytes that are interspersed in hematopoietic tissue regions. Mainly located in proximal bones, rBMAs are smaller

in size and their number can vary depending on physiological conditions and hematopoietic demand [26••].

Various human conditions, including bone disease, hematological malignancies, diabetes, and dietary intake, can modulate the amount of rBMAs within the marrow. In turn, cBMAs are much more stable and only contract upon extreme CR, when they delipidate and the bone marrow matrix is substituted by extracellular mucopolysaccharides in a process denominated gelatinous transformation of the marrow, a histological finding often associated with caquexia [27, 28]. Overall, these results suggest that BMA function varies depending on anatomical location, and that rBMAT may be more closely related to the regulation of active hematopoiesis. Indeed, the high levels of adiponectin that occur concurrently with an increment of rBMAT are probably involved in the normal and pathological regulation of hematopoiesis, although both negative and positive outcomes have been reported on the direct effect of adiponectin on hematopoietic recovery, lymphopoiesis, and granulopoiesis [18, 29–32]. Specifically, Masamoto and colleagues have shown that adiponectin is able to regulate HSC cycle and promote hematopoietic recovery through enhancing HSC exit from quiescence [33]. The stage of differentiation at which MSCs and marrow preadipocytes start expressing adiponectin at biologically relevant levels is yet to be determined, though, so as to distinguish the effect of mature adipocytes versus their precursors in stress hematopoiesis. Clinical data obtained from patients with hematological malignancies showed decreased adiponectin levels in BM interstitial fluids [34]. Given the reduced BMA mass in hematological malignancies, it has been suggested that a minimal local adiponectin concentration is necessary to guarantee physiological regulation of tumor necrosis factor secretion by macrophages, protecting the niche from chronic exposure to a pro-inflammatory microenvironment, a well-known risk factor for cancer development [35].

Zhou and colleagues have further demonstrated that besides adiponectin, BMA are also able to produce stem cell factor (SCF), a cytokine that binds to the c-Kit receptor on the HSC surface, maintaining their survival and promoting their proliferation [12••, 36]. This cytokine is produced within the BM at very high concentration by a specialized population of stromal cells with pericyte properties known as adventicial reticular cells (ARCs), but also by endothelial cells, osteoblasts, and hematopoietic cells. Although these cell populations can guarantee the survival and proliferation of HSCs in healthy adult BM, the increment of adiposity as defined by Adiponectin-Cre-driven depletion seems necessary for rapid HSC regeneration in injured BM after radiation treatment [12••].

The paracrine role of BMA has been investigated in several prior studies [1, 2, 15]. However, a more intensive effort is still required to establish and characterize the whole secretome of BMA. Moreover, given the difficulty on isolating pure mature adipocytes from marrow tissue, which is highly infiltrated by hematopoietic cells, single cell RNA sequencing will likely contribute to tease apart their apparently contradictory role in HSC support. Indeed, as HSC fate within the BM microenvironment is dependent on BMA signaling, a balance between stimulatory and inhibitory cytokines would be necessary to maintain appropriate regulation of hematopoietic output [37, 38].

If the paracrine signaling of BMA through adipokine and cytokine secretion has been demonstrated in several models, a further cell-cell contact mediated regulation of HSC homeostasis is also likely. A recent study explored the BMA niche through electron microscopy, reconstructing a three-dimensional niche and exploring the connections between BMA and other cell types [39]. It was observed that the membrane of BMA can be in direct contact with up to 20 maturing hematopoietic cells and with further maturing hematopoietic elements such as erythroblast islands. However, this specific connection was observed in only about 30% of cells analyzed, as opposed to the numerous tight junctions observed between ARCs and maturing hematopoietic cells within the BM.

The regulation exerted by cell-to-cell contact mechanisms was further analyzed in an in vitro model developed by Mattiucci et al. [6•]. Human primary BMAs were isolated from the femoral head of patients undergoing hip surgery and cultured in vitro using the ceiling culture method. After obtaining a layer of adherent cells, BMAs were cultured together with primary human isolated CD34+ cells for 5 weeks. CD34+ cells were used for hematopoietic colony forming unit (CFU) assays at the end of the co-culture period, and it was shown that HSCs were still able to proliferate and differentiate, although short-term hematopoietic progenitors were drastically reduced during the first 3 weeks of coculture. This model demonstrated that BMA can maintain the survival and differentiation capability of HSCs after 5 weeks of co-culture in vitro. Individually, BMA were less supportive than BM-MSC, but if included together BMA and BM-MSC exerted a synergistic effect to increase HSC proliferation.

This data supports the notion that BMAs represent an important, functional population within the marrow, and that a balanced microenvironment is required for HSC survival. Significant deviations in the composition of the BM stroma

could favor the formation of niches unsupportive of HSCs. Indeed, if the presence of BMA within the marrow is essential for hematopoietic stem cells, it has also been shown that skeletal regions constitutively enriched in BMA (cMAT) are also poorly vascularized, which in itself negatively affects HSC frequency [3, 12••].

Bone Marrow Adipocytes and Hematopoietic Malignancies

In recent years, the interplay between adipocytes and solid cancer has been revealed, with adipocytes promoting the growth of breast, ovarian, and prostate cancers [40–42].Concerning the relationships between adipocytes and hematological malignancies, it has been recognized that leukemia and myeloma cell lines preferentially engraft into ectopic adipocyte enriched BM. Moreover, peripheral white adipose tissue protects B-ALL and myeloma cells from chemotherapy [43–46].

Bone marrow adipocytes have also been shown to play an active role in the support of neoplastic cells in the bone marrow niche and are now considered a potential therapeutic target.

Shafat et al. examined the adipocyte-leukemia cell interactions to determine if this relationship is essential for the growth and survival of AML. Using in vivo and in vitro models of AML, they have shown that BMAs from the tumor microenvironment support the survival and proliferation of malignant cells from patients with AML. They show that AML blasts alter the metabolic profile of adipocytes to induce phosphorylation of hormone-sensitive lipase and consequently activate lipolysis, which then enables the transfer of fatty acids from adipocytes to AML blasts. In addition, pharmacologically blocking the lipid transfer between bone marrow adipocytes and leukemic blasts through inhibition of FABP4, the fatty acid binding protein necessary for transport of these lipids, decreased tumor survival in vitro and increased survival of leukemic mice in vivo [22].

Lu et al. demonstrated that leukemic cells contributed to the generation of small adipocytes in vitro. They attribute the decrease of free fatty acids (FFA) in adipocytes co-cultured with leukemic cells to FFA transport from adipocytes to leukemic cells, which may consequently promote leukemic cell proliferation. These findings highlight that only these small adipocytes, and not all adipocytes, are correlated with poor prognosis for AML patients. They suggest that small adipocytes in the BM may serve as adverse prognostic factors, potentially disrupting AML-adipocyte interactions as a targeted therapeutic approach for AML [47].

As mentioned above, the biology of BM adipocytes can vary on the basis of their anatomical location. Recent evidence of human hematopoietic systems derived from mouse models show that adipocytes situated within regions of hematopoietically active "red" marrow provide important support to regenerating blood populations [12••]. Unlike "yellow" marrow and peripheral adipose depots, red BM experiences a consistent accumulation of newly formed adipocytes under homeostatic conditions [26••, 48]. Boyd et al. observed in both patients and surrogate clinical models that AML disrupts the adipocytic niche in BM. Leukemic suppression of BM adipocytes led to imbalanced regulation of endogenous hematopoietic stem and progenitor cells, resulting in impaired myelo-erythroid maturation. Moreover, they showed that in vivo administration of PPAR agonists induced BM adipogenesis, which rescued healthy hematopoietic maturation while repressing leukemic growth [49••]. In addition, Cahu et al. investigated different BM sites and their control on leukemia development. They focused on constitutive adipocyte-rich or adipocyte-poor (and inversely hematopoietic-poor and hematopoietic-rich, respectively) BM and studied whether T-ALL cells exhibit niche-specific genomic, phenotypic, and proliferative features. Using mouse thoracic vertebrae versus tail vertebrae, as respective BM models of constitutive adipocyte-poor and adipocyte-rich BM, they demonstrate that these two BM microenvironments imprint niche-specific characteristics on T-ALL cells, associated with modified cell-cycle and metabolism-related chemo-resistance. Altogether, these results demonstrate that BM sites differentially orchestrate T-ALL propagation, stamping specific features to leukemic cells such as quiescence and decreased response to cell cycle-dependent chemotherapy [23••].

In conclusion, it is becoming increasingly evident that BMA are capable of influencing the BM microenvironment and hematopoiesis, and consequently tumor cell behavior by providing non-cell autonomous survival capacity for leukemic cells independently of their cell-intrinsic genetics.

As such, elucidating the relationship between BMA and leukemic cells represents a unique opportunity to explore novel therapeutic strategies for the treatment of hematological malignancies.

Acknowledgements The authors thank Daniel Naveed Tavakol for his editing help.

We also thank the "BONEAhead" initiative for making our collaboration possible.

Compliance with Ethical Standards

Conflict of Interest Domenico Mattiucci and Antonella Poloni declare no conflicts of interest; Olaia Naveiras reports having a related patent US13264423 issued.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Gimble M, Robinson CE, Wu X, Kassem M. The function of adipocytes in the bone marrow stroma: an update. Bone. 1996;19:421–8.
2. Hardouin P, Pansini V, Cortet B. Bone marrow fat. Joint Bone Spine. 2014;81:313–9.
3. Naveiras O, Nardi V, Wenzel PL, Hauschka PV, Fahey F, Daley GQ. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. Nature. 2009;460:259–63.
4. Tuljapurkar SR, McGuire TR, Brusnahan SK, Jackson JD, Garvin KL, Kessinger MA, et al. Changes in human bone marrow fat content associated with changes in haematopoietic stem cell numbers and cytokine levels with aging. J Anat. 2011;219:574–81.
5. •• Ambrosi TH, Scialdone A, Graja A, Gohlke S, Jank AM, Bocian C, et al. Adipocyte in the bone marrow during obesity and aging impairs stem cell-based haematopoietic and bone regeneration. Cell Stem Cell. 2017;20(6):771–84. **This paper defines a stem cell-like population that gives rise to osteogenic progeny and promotes haematopoietic reconstitution. Aging and high-fat diet reprogram the mesenchymal lineage to preferentially give rise to adipogenic cells that impair haematopoietic and bone regeneration.**
6. • Mattiucci D, Maurizi G, Izzi V, Cenci L, Ciarlantini M, Mancini S, et al. Bone marrow adipocytes support hematopoietic stem cell survival. J Cell Physiol. 2018;233(2):1500–11. **This work demonstrates that bone marrow adipocytes in vitro were able to maintain the survival and the differentiation capability of haematopoietic stem cells after long term culture.**
7. Poloni A, Maurizi G, Serrani F, Mancini S, Zingaretti MC, Frontini A, et al. Molecular and functional characterization of human bone marrow adipocytes. Exp Hematol. 2013;41:558–66.
8. Corre J, Planat-Benard V, Corberand JX, Pénicaud L, Casteilla L, Laharrague P. Human bone marrow adipocytes support complete myeloid and lymphoid differentiation from human CD34 cells. Br J Haematol. 2004;127:344–7.
9. Di Mascio L, Voermans C, Uqoezwa M, Duncan A, Lu D, Wu J, et al. Identification of adiponectin as a novel hemopoietic stem cell growth factor. J Immunol. 2007;178:3511–20.
10. Gainsford T, Willson TA, Metcalf D, Handman E, McFarlane C, Ng A, et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. Proc Natl Acad Sci U S A. 1996;93:14564–8.
11. Laharrague P. Human subcutaneous adipose cells support complete differentiation but not self-renewal of hematopoietic progenitors. J Cell Physiol. 2006;208:282–8.
12. •• Zhou BO, Yu H, Yue R, Zhao Z, Rios JJ, Naveiras O, et al. Bone marrow adipocytes promote the regeneration of stem cells and haematopoiesis by secreting SCF. Nat Cell Biol. 2017;19(8):891–903. **This work demonstrates that bone marrow adipocytes can produce the Stem Cell Factor and maintain HSC survival and proliferation.**
13. Spindler TJ, Tseng AW, Zhou X, Adams GB. Adipocytic cells augment the support of primitive hematopoietic cells in vitro but have no effect in the bone marrow niche under homeostatic conditions. Stem Cells Dev. 2014;23(4):434–41.
14. Sanchez-Gurmaches J, Guertin DA. Adipocyte lineages: tracing back the origins of fat. Biochim Biophys Acta. 2014;1842:340–51.
15. Hardouin P, Rharass T, Lucas S. Bone marrow adipose tissue: to be or not to be a typical adipose tissue? Front Endocrinol. 2016;7:85.
16. Devlin MJ. Why does starvation make bones fat? Am J Hum Biol. 2011;23(5):577–85.
17. Tavassoli M. Differential response of bone marrow and extramedullary adipose cells to starvation. Experientia. 1974;30(4):424–5.
18. Cawthorn WP, Scheller EL, Learman BS, Parlee SD, Simon BR, Mori H, et al. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. Cell Metab. 2014;20:368–75.
19. Abella E, Feliu E, Granada I, Millá F, Oriol A, Ribera JM, et al. Bone marrow changes in anorexia nervosa are correlated with the amount of weight loss and not with other clinical findings. Am J Clin Pathol. 2002;118(4):582–8.
20. Cawthorn WP, Scheller EL, Parlee SD, Pham HA, Learman BS, Redshaw CM, et al. Expansion of bone marrow adipose tissue during caloric restriction is associated with increased circulating glucocorticoids and not with hypoleptinemia. Endocrinology. 2016;157(2):508–21.
21. Vande Berg BC, Malghem J, Lecouvet FE, Lambert M, Maldague BE. Distribution of serouslike bone marrow changes in the lower limbs of patients with anorexia nervosa: predominant involvement of the distal extremities. Am J Roentgenol. 1996;166(3):621–5.
22. Shafat MS, Oellerich T, Mohr S, Robinson SD, Edwards DR, Marlein CR, et al. Leukemic blasts program bone marrow adipocytes to generate a protumoral microenvironment. Blood. 2017;129(10):1320–32.
23. •• Cahu X, Calvo J, Poglio S, Prade N, Colsch B, Arcangeli ML, et al. Bone marrow sites differently imprint dormancy and chemoresistance to T-cell acute lymphoblastic leukemia. Blood Adv. 2017;1(20):1760–72. **This work, using murine bone marrow models of constitutive adipocyte-poor and –rich BM, demonstrates that these two microenvironments imprint niche-specific characteristics on T-ALL cells.**
24. Schofield R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood Cells. 1978;4(1–2):7–25.
25. Tavassoli M. Marrow adipose cells. Histochemical identification of labile and stable components. Arch Pathol Lab Med. 1976;100:16–8.
26. •• Scheller EL, Doucette CR, Learman BS, Cawthorn WP, Khandaker S, Schell B, et al. Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues. Nat Commun. 2015;6:7808. **This paper demonstrated that bone marrow adipocytes in the distal skeleton are different in morphology and function from the adipocytes located in the proximal bones, respectively part of the constitutive Marrow Adipose Tissue (cMAT) and regulated Marrow Adipose Tissue (rMAT). Adipocytes in the latter are smaller in size and their number can vary, depending on physiological condition of the organism.**
27. Michael P. Gelatinous degeneration of the bone marrow. J Pathol. 1930;33(3):533–8.
28. Böhm J. Gelatinous transformation of the bone marrow: the spectrum of underlying diseases. Am J Surg Pathol. 2000;24(1):56–65.
29. Crawford LJ, Peake R, Price S, Morris TC, Irvine AE. Adiponectin is produced by lymphocytes and is a negative regulator of granulopoiesis. J Leukoc Biol. 2010;88(4):807–11.
30. Yokota T, Meka CS, Kouro T, Medina KL, Igarashi H, Takahashi M, et al. Adiponectin, a fat cell product, influences the earliest lymphocyte precursors in bone marrow cultures by activation of the cyclooxygenase-prostaglandin pathway in stromal cells. J Immunol. 2003;171(10):5091–9.
31. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N. Adiponectin, a new member of the family of soluble defense

collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood. 2000;96(5):1723–32.
32. Masamoto Y, Arai S, Sato T, Yoshimi A, Kubota N, Takamoto I, et al. Adiponectin enhances antibacterial activity of hematopoietic cells by suppressing bone marrow inflammation. Immunity. 2016;44(6):1422–33.
33. Masamoto Y, Arai S, Sato T, Kubota N, Takamoto I, Kadowaki T, et al. Adiponectin enhances quiescence exit of murine hematopoietic stem cells and hematopoietic recovery through mTORC1 potentiation. Stem Cells. 2017;35(7):1835–48.
34. Lin FY, Wu HC, Cheng KC, Tung CL, Chang CP, Feng YH. Adiponectin is down-regulated in bone marrow interstitial fluid in hematological malignancy. Int J Hematol. 2015;102(3):312–7.
35. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30(7):1073–81.
36. Broudy VC. Stem cell factor and hematopoiesis. Blood. 1997;90(4):1345–64.
37. Gainsford T, Willson TA, Metcalf D, Handman E, McFarlane C, Ng A, et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. Proc Natl Acad Sci U S A. 1996;93:14564–8.
38. Camacho V, McClearn V, Patel S, Welner RS. Regulation of normal and leukemic stem cells through cytokine signaling and the microenvironment. Int J Hematol. 2017;105(5):566–77.
39. Robles H, Park S, Joens MS, Fitzpatrick JAJ, Craft CS and Scheller EL. Characterization of the bone marrow adipocyte niche with three-dimensional electron microscopy. Bone 2018:S8756–3282(18)30020–30026.
40. Manabe Y, Toda S, Miyazaki K, Sugihara H. Mature adipocytes, but not preadipocytes, promote the growth of breast carcinoma cells in collagen gel matrix culture through cancer-stromal cell interactions. J Pathol. 2003;201(2):221–8.
41. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med. 2011;17(11):1498–503.
42. Hardaway AL, Herroon MK, Rajagurubandara E, Podgorski I. Marrow adipocyte-derived CXCL1 and CXCL2 contribute to osteolysis in metastatic prostate cancer. Clin Exp Metastasis. 2015;32(4):353–68.
43. Sheng X, Tucci J, Parmentier JH, Ji L, Behan JW, Heisterkamp N, et al. Adipocytes cause leukemia cell resistance to daunorubicin via oxidative stress response. Oncotarget. 2016;7(45):73147–59.
44. Behan JW, Yun JP, Proektor MP, Ehsanipour EA, Arutyunyan A, Moses AS, et al. Adipocytes impair leukemia treatment in mice. Cancer Res. 2009;69(19):7867–74.
45. Ehsanipour EA, Sheng X, Behan JW, Wang X, Butturini A, Avramis VI, et al. Adipocytes cause leukemia cell resistance to L-asparaginase via release of glutamine. Cancer Res. 2013;73(10):2998–3006.
46. Liu Z, Xu J, He J, Liu H, Lin P, Wan X, et al. Mature adipocytes in bone marrow protect myeloma cells against chemotherapy through autophagy activation. Oncotarget. 2015;6(33):34329–41.
47. Lu W, Wan Y, Li Z, Zhu B, Yin C, Liu H, et al. Growth differentiation factor 15 contributes to marrow adipocyte remodeling in response to the growth of leukemic cells Growth differentiation factor 15 contributes to marrow adipocyte remodeling in response to the growth of leukemic cells. J Exp Clin Cancer Res. 2018;37:66.
48. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature. 2008;453:783–7.
49.•• Boyd AL, Reid JC, Salci KR, Aslostovar L, Benoit YD, Shapovalova Z, et al. Acute myeloid leukaemia disrupts endogenous myelo-erythropoiesis by compromising the adipocyte bone marrow niche. Nat Cell Biol. 2017;19(11):1336–47. **This work shows that AML disrupts the adipocytic niche in the bone marrow, leading to imbalanced regulation of endogenous haematopoietic stem and progenitor cells and resulting in impaired myelo-erythroid maturation.**