Bone Marrow Adipocytes

Bone marrow adipocytes are scattered throughout the hematopoietic or "red" marrow, or are densely packed in the marrow cavity, creating "yellow" marrow.

1. Introduction

Bone cancer is one of the most destructive and painful manifestations of malignancy, and is often terminal for patients with tumors that originate in other locations and disseminate through the bloodstream to the bone marrow. Bone cancers can also result from a primary tumor within the bone, such as an osteosarcoma, or a hematopoietic malignancy that originates either within the bone marrow or elsewhere in the blood or lymph nodes, such as multiple myeloma, lymphoma, or leukemia.

2. BMAT and Multiple Myeloma

Aging and obesity are now well-known risk factors for multiple myeloma (MM), a blood cancer of the plasma cell, as well as its precursor disease, monoclonal gammopathy of undefined significance (MGUS)[51]. As obesity and aging also cause increases in BMAT, researchers have asked the logical question: does BMAT contribute to the risk of MM or contribute to the disease progression? A major question in the field is if and how aging, through effects on the BM niche, contributes to increased cancer risk (independent from increasing mutational burden within cells[52] and weakening the immune system[42]). This question is especially relevant in MM, where aging is a major risk factor and driver mutations are diverse and evolve chronologically and spatially[53].

The review "Signaling Interplay between Bone Marrow Adipose Tissue and Multiple Myeloma Cells"[54] provided an overview of the field of myeloma and BMAT in 2016. Since then, more evidence has demonstrated the many ways in which BMAds support myeloma cells. The Yang laboratory found that mature adipocytes in bone marrow protect myeloma cells against chemotherapy through autophagy activation[30] and that myeloma-associated adipocytes contribute to bone disease[48] through PPARγ, EZH2, and PRC2-related mechanisms. Moreover, they demonstrated that myeloma cells can shift the balance from osteoblastogenesis to adipogenesis through inhibiting the ubiquitin ligase MURF1 in MSCs[55]. This laboratory also found that the adipocyte-derived factor, resistin, induces multidrug resistance in MM cells by inhibiting cell death and upregulating the ABC transporter protein expression[56].

Leptin is a known pro-myeloma adipokine factor that is also increased in obesity. Analysis of leptin levels in humans identified significantly higher leptin in MM patients compared with normal controls, and found that leptin levels were positively correlated with MM clinical stage and other clinical predictors[31]. Not only does leptin support MM cell proliferation and reduced toxicity of bortezomib[31], but it also counteracts the anti-tumoral activity of invariant natural killer T (iNKT) cells, which express the leptin receptor [34]. Thus, leptin appears to both directly support tumor cells and indirectly support them through effects on the immune system, suggesting that targeting this obesity-related factor, either through decreasing obesity or blocking leptin–leptin receptor signaling, could be a promising therapy in MM or other obesity-related cancers.

Other adipokines, such as apelin[57] and chemerin[58], are suggested as diagnostic markers for MM, although the potential for targeting them therapeutically is unknown. IL−6 is one of the most well-known pro-myeloma adipokines, and targeting of IL6 signaling is under clinical investigation with monoclonal antibodies to *IL−6* (siltuximab) or the IL−6 receptor (tocilizumab)[59]. CCL2/monocyte chemotactic protein−1 (MCP−1) is an adipokine that promotes macrophage-associated chemoresistance in MM by shifting macrophages towards the M2-like phenotype[58]. Targeting nicotinamide

phosphoribosyltransferase (visfatin) in tumor cells themselves using siRNA transfection has recently been shown to reduce cell proliferation and induce apoptosis, however the potential advantage of inhibiting visfatin derived from local or distant adipocytes is not known[39].

The role of fatty acid metabolism in MM has recently been reviewed[60], and researchers are currently exploring if targeting fatty acid metabolism in MM cells basally or when in co-culture with BMAT is a viable new therapeutic target. Evidence suggests that omega-3 fatty acids may have anti-myeloma effects via induction of apoptosis through both mitochondrial and cell death receptor pathways[61] or by reducing MM exosome-mediated suppression of natural killer (NK) cell cytotoxicity[62]. Similarly, arachidonic acid, a biologically active fatty acid, can induce apoptosis in chronic myeloid leukemia (CML) cells[63], and may induce ferroptosis-mediated cell death in MM[63]. However, other fatty acids may support myeloma cells through acting as inflammatory mediators or as a fuel source for MM cells, as has been seen in melanoma[64], and thus targeting fatty acid metabolism (for example with Triacsin C, an ACSL inhibitor) may represent a novel way to inhibit tumor cells[65]. In addition to targeting fatty acid metabolism, our laboratory has recently found that targeting fatty acid transport or uptake proteins may be another way to impede growth or drug resistance evolution in MM[26][66].

The Edwards laboratory recently built on their previous findings by demonstrating that myeloma cells downregulate the anti-myeloma protein adiponectin via TNFα[67]. This study also demonstrated an increase in BMAT in early disease or low tumor burden in mice[67], implicating a potential role for MM cells in accelerating adipogenic differentiation of progenitors. However, a recent study published by Mehdi et al. utilizing single-cell RNA-Seq suggests that myeloma-patient-derived MSCs are functionally quiescent and exhibit gene expression profiles consistent with impaired adipogenesis and enhanced angiogenesis compared to MSCs from normal donors[68]. These authors also identified a novel IGFBP2+-expressing population of small adipocytes that is suppressed in MM, which may contribute to reduced osteoblast differentiation and the vicious cycle of MM-induced bone disease. Our laboratory[22], as well as the Edwards laboratory[67], have found that BMAds shrink in the later stages of myeloma progression and that MM cells can have differing effects on adipogenesis based on tumor cell type or culture conditions[69]. We have also now demonstrated a senescence-associated secretory phenotype (SASP) in local adipocytes exposed to MM cells[22], adipocytes exposed before differentiation to MM cells[69], and in MSCs exposed to MM cells or from MM patients[70]. SASP proteins such as IL-6 can stimulate proliferation or drug resistance in myeloma cells, and thus targeting senescent bone marrow cells or senescence in general in the bone marrow niche represents a potential novel therapeutic target for MM patients. Table 2 summarizes ways in which myeloma cells and other tumor cells can hijack and modulate BMAds.

Table 2. Factors and mechanisms through which BMAds are affected by tumor cells.

Factors	Example	References
Induction of Lipolysis (Shrinking of Adipocytes)	**Adipose triglyceride lipase (ATGL) and phosphorylation and activation of hormone-sensitive lipase (HSL)**	[32][71][72]
Induction of Senescence-Associated Secretory Phenotype	**IL6, CXCL1, CXCL2**	[22]
Pro-Tumor Factors	**COX−2 and MCP−1**	[73]
Decreased Anti-Tumor Hormones	**Adiponectin**	[67]
Mature Adipocyte Size Can Increase in Early Stages of Disease. MSCs Skewed from Osteogenesis to Adipogenesis.	**α4 integrin subunit on MM cells stimulating VCAM1 On MSCs causing activation of Pkcβ1 signaling and repression of the muscle ring-finger protein−1 (MURF1)-mediated ubiquitylation of Pparγ2**	[23][55][67]

4. BMAT and Breast and Prostate Cancer

A recent review has discussed the roles of BMAds (and leptin, adiponectin, and Sam68 specifically) in bone metastasis from breast cancer[19]. There are conflicting results when analyzing the influence of age in the development of bone metastasis for breast cancer patients[74]. Obesity, however, is a strong risk factor for developing breast cancer, and although one study found that obesity had no effect on the recurrence pattern of early breast cancer patients, it did find that obese early breast cancer patients had shorter overall survival compared to their normal-weight counterparts[75]. To analyze the role of BMAds in bone metastasis specifically, the King laboratory has performed elegant work demonstrating that breast cancer cells migrate to BMAds and interact with them closely using human tissue femur explants[76][77]. Using co-injections of breast cancer cells and adipocytes or pre-adipocytes into nude mice, BMP9 was found to inhibit the growth and metastasis of breast cancer cells, which may be in part related to their interaction with pre-adipocytes or adipocytes via leptin signaling[71].

The Podgorski laboratory demonstrated that prostate and breast cancer cells exposed to adipocyte-rich environments increase HO−1, an oxidative stress enzyme, which contributes to tumor growth and invasiveness. Adipocytes also induced expression of the endoplasmic reticulum (ER) chaperone BIP and splicing of XBP1, indicating adipocyte-driven unfolded protein response, which was sensitive to antioxidant treatment. Survivin expression in tumor cells was found to contribute to tumor cell survival in response to oxidative and ER stress or HO-1 induction by adipocyte exposure[33]. This laboratory also demonstrated the importance of using 3D culture systems wherever possible to co-culture adipocytes and prostate cancer cells, similar to what we have seen in BMAT and myeloma 3D cultures[13], to create a more physiologically relevant culture system[78]. Recently, the Podgorski laboratory demonstrated that prostate tumor cell-derived IL1β can induce an inflammatory phenotype in BMAds and decrease sensitivity to docetaxel via lipolysis-dependent mechanisms[78]. This team also observed that CXCL1 and CXCL2 derived from BMAds contribute to osteolysis in metastatic prostate cancer[79]. These data suggest that BMAds contribute to cancer-associated bone disease, which is a very interesting avenue to pursue.

The Podgorski laboratory also found that BMAds promote a Warburg phenotype (i.e., extensive glycolysis even in the presence of oxygen) in metastatic prostate tumors via HIF-1α activation and demonstrated that the lipolytic enzymes Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are upregulated in BMAds exposed to prostate cancer cells, which paralleled a release of FFAs from the BMAds[32]. Although all FFAs can act as a fuel source for FAO, the nature and properties of the FFA released from BMAds may be very important, as inflammatory fatty acids may specifically increase prostate cancer bone metastasis. For example, Wang et al. found that the total level of FFAs and caprylic acid (C8:0) were significantly higher in prostate cancer patients with bone metastases, and demonstrated in vitro with co-culture systems that caprylic-acid-treated adipocytes promoted the invasion and migration of prostate cancer cells[78]. As described with MM above, alterations in lipid metabolism are also observed in breast tumors at both the cellular and tissue levels[80]. Targeting lipid metabolism in cancer cells in the bone marrow holds great promise, but more analyses (specifically metabolic flux, proteomic or lipidomic mass spectrometry, gene expression, and functional outputs) are needed in tumor cells treated with different FFAs before safely and effectively targeting fatty acid metabolism in preclinical and clinical settings can become a reality.

5. BMAT and Leukemia

Data are accumulating showing that leukemic cells are also protected from chemotherapy-induced cytotoxicity when in close proximity to BMAds through an array of mechanisms. This topic has been specifically covered in a comprehensive review from Dr. Fischer-Posovszky's group[42], in which they raise the question about the role of BMAds with the title "Adipocytes in Hematopoiesis and Scute Leukemia: Friends, Enemies, or Innocent Bystanders?". It appears that BMAds have temporally and disease-state-dependent roles in acute myeloid leukemia (AML) progression and myelo-erythroid maturation. Adipocytes can sequester and metabolize the chemotherapy daunorubicin[42], and this is in part due to a complex loop whereby adipocytes protect acute lymphoblastic leukemia (ALL) cells from oxidative-stress-induced cell death (which can also be mimicked by treating the cells with antioxidants), while ALL cells induce oxidative stress in adipocytes, which leads to their secretion of pro-survival factors that protect tumor cells from daunorubicin[42]. The team also found that glutathione synthesis is partially the cause of BMAd protection of ALL cells[42].

However, leukemic suppression of BMAds has also been shown by Boyd et al. to lead to imbalanced regulation of endogenous hematopoietic stem and progenitor cells, resulting in impaired myelo-erythroid maturation[72]. This team found that in vivo administration of PPARγ agonists induced BM adipogenesis, which rescued healthy hematopoietic maturation while repressing leukemic growth. The study was the first to identify an unappreciated axis between BM adipogenesis and normal myelo-erythroid maturation that could potentially have therapeutic implications for BM failure in AML by non-cell autonomous targeting of the niche[72].

Similarly to that described in later stage MM, AML patients have been found to have fewer and smaller adipocytes in their BM sections, as based on perilipin immunohistochemistry (IHC), compared to controls[81]. An adverse effect of smaller adipocytes on AML patient prognosis has been observed[82]. Similarly to that described in other cancers, FABP4 appears to be a potential target in AML, as it promotes AML aggressiveness through enhanced DNMT-1-dependent DNA methylation[83][84]. The Shi group also found that leukemic cells can produce growth differentiation factor 15 (GDF15), which remodels the residual BMAds into small adipocytes and is associated with a poor prognosis in AML patients, and that transforming growth factor-β type II receptor (TGFβRII) is the main receptor for GDF15 on BMAds[71]. They showed that transient receptor potential vanilloid (TRPV) channels negatively regulated GDF15-induced remodeling of BMAds, and found that GDF15 reduced the expression of the transcription factor Forkhead box C1 (FOXC1) in BMAds[71]. Shafat et al. demonstrated that AML blasts program BMAds to generate a protumoral microenvironment as well[85]. AML cells induced adipocyte lipolysis of triglycerides via increased HSL activity, which released FFAs. Upregulated FABP4 in both

AML cells and adipocytes was observed when they were in co-culture, which increased tumor cell proliferation, as validated by short hairpin RNA knockdown experiments [85]. They also found that inhibiting CPT1A in an AML-patient-derived xenograft model improved mouse survival[85], again supporting that fatty acid metabolism is a pro-survival metabolic pathway for tumor cells in the bone marrow. Also in AML, Tabe et al. demonstrate that tumor cells are protected from spontaneous apoptosis via upregulation of FAO and from increased AMP-activated protein kinase (AMPK) signaling resulting from FFA transfer from BMAds[28]. The recent review by this group is an excellent resource on this topic and highlights the recent progress in our understanding of fatty acid metabolism in AML cells in the adipocyte-rich BM microenvironment[71].

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