The Role of Adipokines and Bone Marrow Adipocytes in Breast Cancer Bone Metastasis

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Abstract: The morbidity and mortality of breast cancer is mostly due to a distant metastasis, especially to the bone. Many factors may be responsible for bone metastasis in breast cancer, but interactions between tumor cells and other surrounding types of cells, and cytokines secreted by both, are expected to play the most important role. Bone marrow adipocyte (BMA) is one of the cell types comprising the bone, and adipokine is one of the cytokines secreted by both breast cancer cells and BMAs. These BMAs and adipokines are known to be responsible for cancer progression, and this review is focused on how BMAs and adipokines work in the process of breast cancer bone metastasis. Their potential as suppressive targets for bone metastasis is also explored in this review.

Keywords: bone marrow; adipokines; adipocyte; bone metastasis; breast cancer

1. Introduction

Breast cancer is the most frequently found cancer in the female population and also one of the most prevalent causes of cancer-related deaths [1]. Despite recent advances in breast cancer treatment, it still poses an important health problem for women worldwide. The morbidity and mortality of breast cancer are mostly due to a distant metastasis, which most often occurs in the lung, liver, brain and bone [2,3]. Among these frequent sites of breast cancer metastasis, bone metastasis occurs in about two thirds of advanced breast cancer patients and leaves them with an expected survival of two to three years [4,5]. The “seed and soil hypothesis” explains the mechanism by which a certain primary cancer metastasizes to a specific organ, and according to this theory, the breast cancer cell is the “seed” and the bone is the “soil” in cases of breast cancer with bone metastasis [6]. Therefore, breast cancer cells and bone are major factors involved throughout the process of bone metastasis in breast cancer, and bone marrow adipocyte (BMA) is one of the bone factors in the bone microenvironment. Both BMAs and breast cancer cells secrete adipokines, and this review is focused on how BMAs and adipokines are involved in the process of breast cancer bone metastasis and how they can work as potential suppressive targets of bone metastasis.

2. Basics of Adipokines

Adipokines are metabolites, lipids, and bioactive peptides secreted by adipose tissue, and there more than 600 adipokines have been discovered to date, including batokines and lipokines [7–9]. Adipose tissue is composed of adipocytes, pre-adipocytes, fibroblasts, macrophages, stromal cells, endothelial cells and monocytes [10]. Thus, adipokines can be secreted by these different kinds of cells comprising adipose tissue, and most adipokines are reported to be secreted by cells other than mature adipocytes [11]. Adipokines are generally involved in appetite control, fat distribution, insulin secretion, energy expenditure, inflammation and blood pressure [12]. As for the role of adipokines in...
cancer, cancer cells express adipokine receptors, through which adipokines play their role in cancer cells. [13]. Adipokines can be grouped into pro-inflammatory types (leptin, tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), haptoglobin, IL-8, IL-1β, fibrinogen, resistin, apelin, chemerin, granzyme B, visfatin, lipocalin-2, WNT1-inducible-signaling pathway protein 1 (WISP1), dipeptidyl peptidase-4 (DPP4), vascular adhesion protein-1 (VAP-1) and retinol-binding protein 4 (RBP4)) and anti-inflammatory types (adiponectin, angiopoietin 2, omentin-1, vaspin, nesfatin, secreted frizzled-related protein 5 (SFRP5) and C1q/TNF-related proteins (CTRPs)) [14–16]. These various adipokines can have an effect on the development of breast cancer and its growth, progression and metastasis (review [17,18]), and their representative roles in breast cancer are listed in Table 1.

| Table 1. Summary of the roles of adipokines in breast cancer biology. |
|---------------------------------------------------------------|
| **Adipokines** | **Roles in Breast Cancer** |
| Leptin | promotes breast cancer cell proliferation by JAK-STAT, ERK1/2, AKT-GSK3 and PKC-α pathways [19,20] <br> enhances breast cancer progression through the increase of cyclin D1, and CDK2 and by the decrease of p21, p27 and p53 [20–22] <br> reduces breast cancer cell apoptosis by increasing survivin and bcl-2 and decreasing caspase-9 [21,22] <br> enhances breast cancer cell migration and invasion through ACAT2 upregulation by PI3K/AKT/SREBP2 pathway [24] <br> elevates angiogenesis by upregulating VEGF and Notch signaling [25,26] <br> increased leptin in adipose stromal cells leads to the expression of EMT- and metastasis-related genes [27] |
| Adiponectin | reduces breast cancer cell growth by inactivating p44/p42 MAPK, activating AMPK pathway, and inhibiting Akt phosphorylation [28] <br> induces breast cancer cell apoptosis through downregulating bcl-2 and upregulating p33, Bax and caspase 8 [29,30] <br> induces autophagy related cell death by STK11/LKB1-AMPK-ULK1 pathway [31] <br> Globular adiponectin promotes breast cancer cell invasion by autophagy [32] <br> inhibits metastatic process by upregulation of LKB1 through AMPK-S6K axis activation [33] <br> Globular adiponectin supports initial metastatic progression through autophagy activation [34] |
| Autotaxin (ATX) | induces invasion and motility of breast cancer cells by gp130/JAK/STAT3 pathway [35] <br> LPA, an ATX receptor, stimulates breast cancer cell migration by PI3K, PAK1 and MAPK pathways [36] <br> Overexpression of ATX-LPA signaling promotes osteolytic bone metastasis of breast cancer cells [37] <br> induces EMT of breast cancer cells by STAT3 pathway [38] <br> associated with breast cancer stem cell self-renewal through the upregulation of Sox, c-Myc and Nanog [39] |
| IL-6 | enhances the metastatic potential of breast cancer by EMT, and stemness [41] <br> promotes breast cancer metastasis by phosphorylation of ezrin, radixin and moesin complex [42] <br> High expression of resistin in breast cancer is associated with poor prognosis [43,44] |
| IL-8 | IL-8 overexpression promotes cell migration via PI3K-AKT signaling pathway and EMT in triple-negative breast cancer [45] <br> activates breast cancer-associated adipocytes (CAAs) and promotes tumorigenic effects of CAA [46] <br> associated with early steps of breast cancer cell dissemination by adipocytes [47] <br> activates osteoclastogenesis through CXCR1 receptor and promotes osteolytic bone metastasis in breast cancer [48] |
| IL-11 | associated with stemness and metastasis in breast cancer [49] <br> promotes osteoclastogenesis by sustaining the pool of osteoclast progenitor cells [50] <br> involved in breast cancer bone metastasis through gp130/STAT3 pathway [51] <br> activates osteoclastogenesis through JAK1/STAT3 pathway and promotes osteolytic bone metastasis [52] |
| IGFBP2 | IGFBP2 overexpression is associated with breast cancer proliferation, invasion and migration [53] <br> IGFBP2 overexpression is associated with breast cancer lymph node metastasis [54,55] <br> induces metastatic bone colonization by endothelium recruitment through interaction with IGF type-I receptor [56] |
| TGF-β | facilitates breast cancer migration and invasion through Smad3 and ERK5 signaling pathways [57] <br> suppresses the antitumor function of ROR1-CAR T-cells against TNBC [58] <br> promotes breast cancer progression by TWIST expression [59] <br> induces bone metastasis by stimulating breast cancer cells to secrete PTHrP and IL-11 [60,61] <br> stimulates breast cancer cells to secrete PTHrP to activate osteoclasts that increase bone resorption and promote tumor cell proliferation and survival [62] |
ATX, COX-2 associated with tumor cell adhesion, migration and invasion in breast cancer by binding to integrins

Oncostatin M (OSM) promotes metastasis in breast cancer through pre-vascular event and increased circulating tumor cells

OSM expression is correlated with breast cancer progression by JAK/STAT pathway

OSM expression is correlated with mesenchymal and stem cell-like differentiation in breast cancer by PI3K pathway

High expression of OSM in breast cancer is associated with poor prognosis by estrogen receptor downregulation

activates osteoclastogenesis through AREG autocrine pathway to induce osteolytic bone metastasis

associated with breast cancer development. However, this is not the simple criteria of overweight based on BMI; rather, suggested that obesity, which is due to an increased number and size of adipocytes, is associated with breast cancer prognosis

IL-1β drives breast cancer growth and bone metastasis

MIF promotes breast cancer cell proliferation by activation of PI3K/AKT signaling pathway

Cathepsin K associated with breast cancer cell proliferation and metastasis

CCL2/MCP-1 CCL2/CCR2 chemokine signaling promotes breast cancer growth and invasion

CCL2-induced chemokine cascade promotes breast cancer metastasis by increased recruitment of metastasis-associated macrophages

CXCL1 promotes breast cancer migration, invasion, stem cells subpopulations, EMT, or mammosphere formation

VEGF stimulates breast cancer cell migration in conjunction with cystathionine-γ-lyase

VEGF stimulates breast cancer cell migration by filopodia formation via NRP1

TNFa induces trastuzumab resistance in HER2-positive breast cancer cell by MUC4 expression

Table 1. Cont.

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| Adipokines | Function |
|------------|----------|
| Oncostatin M (OSM) | promotes metastasis in breast cancer through pre-vascular event and increased circulating tumor cells |
| Osteopontin (OPN) | associated with tumor cell adhesion, migration and invasion in breast cancer by binding to integrins |
| Pentraxin 3 (PTX3) | increases cancer cell migration, macrophage migration to cancer cells and osteolysis, formation, which result in osteolytic bone metastasis |
| IL-1B | drives breast cancer growth and bone metastasis |
| MIF | promotes breast cancer cell proliferation by activation of PI3K/AKT signaling pathway |
| Cathepsin K | associated with breast cancer cell proliferation and metastasis |
| CCL2/MCP-1 | CCL2/CCR2 chemokine signaling promotes breast cancer growth and invasion |
| CXCL1 | promotes breast cancer migration, invasion, stem cells subpopulations, EMT, or mammosphere formation |
| VEGF | stimulates breast cancer cell migration in conjunction with cystathionine-γ-lyase |
| TNFa | induces trastuzumab resistance in HER2-positive breast cancer cell by MUC4 expression |

3. Origin of Adipokines in the Process of Breast Cancer Bone Metastasis

Adipokines are variably involved in the process of breast cancer development, progression and metastasis, and the cells of origin for these adipokines are breast cancer cells and adipocytes. Breast cancer cells have been reported to secrete various adipokines, such as leptin, adiponectin, ATX, COX-2, MMP, cathepsin K, TGF-β, IGFI and VEGF (review [17,18,100]). Adipokines can be subclassified into central adipocytes and local adipocytes. Central or systemic adipocytes in obese patients can undergo changes and secrete adipokines that are altered both quantitatively and qualitatively [101]. Epidemiologic data show that postmenopausal women with obesity have a higher incidence of breast cancer, and obesity is related to breast cancer prognosis [102]. It has been suggested that obesity, which is due to an increased number and size of adipocytes, is associated with breast cancer development. However, this is not the simple criteria of overweight based on BMI; rather,
it is the obesity type and menopause status that have a significant impact on breast cancer development. Obesity is not correlated with breast cancer development before menopause, but hormone-positive breast cancer incidence increments every 5 years after menopause [103]. Moreover, central obesity is related to breast cancer development in pre-menopausal women [104], and it is especially related to the development of triple-negative breast cancer (TNBC) [105–107]. The mechanisms by which central obesity plays a role in breast cancer development are as follows: firstly, the NFκB, JAK, STAT3 and AKT pathways are activated by decreased adiponectin and increased leptin and estrogen in the leptin–adiponectin–estrogen axis; secondly, central adipose tissue induces oxidative stress by increasing the secretion of pro-inflammatory adipokines such as IL-1β, IL-6, IL-8 and TNFα; lastly, central adipose tissue increases the secretion of micro RNA (miRs) that play a role in cancer development, such as miR-23, miR-155, miR-140 and miR-302f, and decreases the secretion of miR-148b, a tumor suppressor miR (review [108]). Therefore, central adipose tissue harbors chronic inflammation and high oxidative stress, a microenvironment strongly resembling that of the tumor microenvironment. Local adipocytes can be further subdivided into breast local adipocytes and BMAs. A total of 56% of breast parenchyma consists of adipose tissue in non-lactating breasts [109] and 35% in lactating breasts [110]. Therefore, adipocytes are invariably juxtaposed with cancer cells in breast cancer, and these adipocytes are called cancer-associated adipocytes (CAAs). CAAs secrete various adipokines that can affect breast cancer progression through interactions with breast cancer cells [111]. The other local adipocytes, BMAs, comprise the bone marrow in various proportions, depending on certain conditions. They generally comprise 70% of the bone marrow volume in average adults [112], and they also secrete various adipocytokines, such as leptin, adiponectin, IL-1β, IL-6, VCAM-1, TNF-α and VEGF [113].

In addition to breast cancer cells and adipocytes, other cell types that secrete adipokines in the process of bone metastasis are bone stromal cells, e.g., osteoblasts and osteoclasts, and cancer-associated fibroblasts (CAFs), which can be differentiated from quiescent fibroblasts. Osteoblasts and osteoclasts secrete TGF-β, IL-6, IL-8, MCP-1, VEGF, IL-1β, cathepsin K, macrophage inflammatory protein 2 (MIP-2) and resistin [114], and breast cancer cells increase the secretion of IL-6, MCP-1 and IL-8 from osteoblasts [115] and also increase the secretion of IL-8, IL-6, MCP-1, MIP-2 and VEGF [116]. CAFs secrete HGF, TGF-β, CXCL12, IL-6, VEGF and MMPs [117]. Among these, CXCL12/14 and IGF-1/2 are expressed at a higher rate in TNBC with bone metastasis than in TNBC without bone metastasis, suggesting CAFs as the source of these adipokines rather than tumor cells [118].

4. Bone Marrow Adipocytes (BMAs)

BMAs had simply been considered one of the components of bone marrow, and only recently has their importance as multifunctional cells surfaced. Various conditions alter the proportion of BMAs within the bone marrow; older age, obesity, malnutrition, drug use and radiation tend to increase the number of adipocytes within the bone marrow [119–122]. BMAs can be subdivided into two types: inducible or regulated BMAs (rBMAs) and constitutive BMAs (cBMAs) [123]. rBMAs can be found in the proximal location of a bone and constitute the red marrow, whereas cBMAs are located in the distal portion and constitute the yellow marrow. These two BMAs differ in development, lipid saturation, gene expression and vascular density [123,124]. BMAs are derived from Sca1+, CD45- and CD31- [125] or LepR+, CD45- and CD31- bone marrow mesenchymal cells [126], which harbor bi-potent progenitor stem cell characteristics and hence can differentiate into either adipocytes or osteoblasts. Some suggest that BMAs can be phenotypically classified into two different types according to their site of origin: BMAs in long bones are of a white phenotype, whereas BMAs in the vertebrae are of a brown phenotype [127]. BMAs are involved in bone remodeling, energy regulation and insulin metabolism by secreting various adipokines, such as hormones, cytokines and fatty acids [128,129]. The secretory profile of BMAs differs from that of adipocytes in other locations; the mRNA expression of leptin and adiponectin is lower in BMAs than in extramedullary adipocytes [130,131], and TNF-α and IL-6 expression is higher in BMAs than in visceral adipocytes [130]. BMAs are also reported to have a high pro-angiogenic and pro-apoptotic profile [132]. Furthermore, BMAs...
carry out diverse functions by releasing various mediators, and, especially in bone remodeling, they secrete leptin and adiponectin in order to promote the differentiation of multipotent stem cells (MSC) into osteoblasts and their proliferation. However, at the same time, BMAs can secrete chemerin in order to suppress osteoblastogenesis [127]. Additionally, BMAs secrete TNF-α and RANKL to promote osteoclastogenesis [127]. BMAs differ from other peripheral tissue adipocytes in location, cellular morphology, the characteristics of the lipid droplets within the cells, and cellular function [133] (Table 2).

Table 2. Difference between bone marrow adipocytes (BMAs) and peripheral tissue adipocytes.

| Parameters       | BMA                  | Peripheral Tissue Adipocyte |
|------------------|----------------------|-----------------------------|
|                  | cBMA                 | rBMA                        |
| Cell shape       | Spherical            | Spherical                   |
|                  | 37-41µm              | 30-36µm                     |
| Cell size        |                      |                             |
|                  | 25-200 µm            | 15-60 µm                    |
|                  | Unilocular           | Multilocular and small      |
| Lipid droplets   |                      |                             |
|                  |                      |                             |
| Location         | Distal site          | Proximal Central endosteal  |
|                  |                      | Subcutaneous                |
| Function         | No response to environmental stimuli | Response to environmental stimuli |
|                  |                      | Store energy in the form of TG |
|                  |                      | Fat consumption in order to maintain body temperature |

5. The Role of Adipokines in Breast Cancer Bone Metastasis

Breast cancer cells undergo following five steps when they metastasize to the bone: (1) invasion and migration, (2) intravascular infiltration and transportation, (3) extravasation, (4) adherence and arrest to the bone matrix, and (5) colonization of the cancer cells and subsequent bone destruction [134]. The first, second and third steps are common in all distant metastases of cancer, but the fourth and fifth steps are bone metastasis-specific processes.

Adipokines are involved in breast cancer progression by binding to the adipokine receptors on breast cancer cells. Firstly, there is a metastasis-associated gene among the 64 genes controlled by leptin [135], which is secreted by the adipose stromal cells. The increased secretion of leptin promotes metastasis by increasing the expression of epithelial–mesenchymal transformation (EMT) and metastasis-associated genes (SERPINE1, MMP-2, and IL-6) in breast cancer cells [136]. MIF, which is secreted by tumor-specific T-cells, is reported to be especially involved in the pre-metastatic niche during the process of bone metastasis by means of intravasion, angiogenesis and EMT in breast cancer circulating tumor cells (CTCs) [82]. ATX–LPA signaling is involved in breast cancer metastasis, but it also promotes osteolytic bone metastasis when LPA1 is overexpressed in the MAD-BO2 breast cancer cell line [37,137]. In addition, IL-11 and IL-8, which are secreted by breast cancer cells, change the osseous environment in order to facilitate osteoclast formation and bone colonization [138,139]. IL-8, which is produced mainly by macrophages, increases osteolytic bone metastasis by activating osteoclastogenesis through the CXCR1 receptor [48]. Breast cancer with bone metastasis shows significantly increased expression of IL-11 in comparison with breast cancer without bone metastasis, and IL-11 is known to be involved in bone metastasis through the gp130/STAT3 pathway [51]. IL-11, secreted from the bone-specific metastatic breast cancer cell line (BoM-1833), promotes osteolytic bone metastasis by activating RANKL-independent osteoclastogenesis through the JAK1/STAT3 pathway [52]. Insulin-like growth factor-binding protein 2 (IGFBP2), secreted by metastatic breast cancer cells, contributes to metastatic bone colonization by interacting with IGF type-1 receptor on endothelial cells through endothelial recruitment [56]. When breast cancer cells are exposed to a stimulated bone environment, IGFBPs show a significant alteration in expression. An increased expression of IGFBP-3 in the bone microenvironment has been reported to facilitate bone metastasis.
by increasing TGF-β-mediated cell proliferation [140]. TGF-β from the bone matrix stimulates breast cancer cells to secrete PTHrP and IL-11 and induces bone metastasis [60,61]. This PTHrP additionally induces tumor cell proliferation and tumor cell survival by increasing bone resorption with osteoclast activation through SMAD-independent and SMAD-dependent pathways [62]. IL-6, MCP-1 and VEGF, which are secreted by osteoblasts, enable cancer cells to colonize and proliferate in the bone microenvironment [116]. Oncostatin M (OSM), a member of the IL-6 family that is secreted by breast cancer cells, facilitates osteolytic bone metastasis by activating osteoclastogenesis via the AREG autocrine pathway [69]. Pentraxin 3 (PTX3) is overexpressed in the bone metastasis of breast cancer when compared with lung, liver and brain metastasis, because PTX3 induces osteolytic bone metastasis by facilitating cancer cell migration and macrophage migration to cancer cells and increasing osteoclast formation [76]. Bone metastasis tends to occur more frequently in breast cancer that has an increased expression of IL-1B when compared with breast cancer that does not (37% vs. 5%) [141]. Breast cancer cell lines that have bone metastasis (MDA-IV) also show an increased expression of IL-1B [142], which is secreted by both breast cancer cells and osteoblasts, and it has been reported that IL-1B promotes bone metastasis by awakening breast cancer cells that are dormant within the bone [78]. VEGF from the bone matrix promotes neovascularization in breast cancer bone metastasis [143], and VEGF secreted by breast cancer cells activates osteoclasts. It is notable that the number of osteoclasts is increased in breast cancer bone metastasis tissue while the expression of VEGF receptor 1 (VEGFR1) is increased in breast cancer tissue [144]. Cathepsin K plays an important role in osteoclast-mediated bone destruction, and it is increased in breast cancer with bone metastasis [85]. Cathepsin K from breast cancer cells activates osteoclasts, which promotes osteolytic bone metastasis [85,86], and cathepsin K from the bone marrow stromal cells promotes breast cancer bone metastasis by splicing and activating SPARC in breast cancer cells [87]. When angiopoietin-2 is overexpressed in ER-positive breast cancer cells that are dormant in the bone marrow (BM) niche, it destabilizes the niche endothelium through endothelial Tie2 receptor and awakens ER-positive breast cancer cells from their dormant states, thus resulting in cancer cell growth [145]. Angiopoietin-like protein 2, secreted by breast cancer cells, increases CXCR4 expression in breast cancer, which increases cross-talk between CXCR4 and CXCL12 and, as a result, recruits breast cancer cells to the bone metastatic site [146]. Basic fibroblast growth factor (FGF) secreted by TGF-β, which originates from BM myeloid cells, activates tumor cell proliferation through the MAPK–ERK pathway by binding to FGFR1 receptors, which increases metastatic bone lesions [147].

While most adipokines promote bone metastasis (Figure 1), there are a few that suppress bone metastasis, namely CCL2/MCP-1, which inhibits bone metastasis by suppressing ICAM-1 expression and anchorage-independent tumor cell growth and cell migration [92].
6. Roles of BMAs in Bone Metastasis of Breast Cancer

Like other adipocytes, BMAs are also involved in breast cancer progression and metastasis, especially bone metastasis. BMAs are usually located in the endosteal surface of the diaphysis and the trabecular bone of the epiphysis and metaphysis, and bone metastasis usually occurs in the latter when active bone remodeling takes place. The bone has two physiologic niches, the endosteal niche and the vascular niche [148]. The endosteal niche is located on the surface of the trabecular and endocortical bone and is composed of osteoblasts and osteoclasts. In this endosteal niche, bone formation and bone resorption by osteoclasts occur [149]. The vascular niche is composed of endothelial cells, pericytes and smooth muscle cells, and it is involved in the recruitment of endothelial precursor cells, mesenchymal stem cells and hematopoietic stem cells [150,151]. In breast cancer patients, the physiologic niche of the bone becomes a metastatic niche through the pre-metastatic niche by means of extracellular matrix remodeling by metastatic carcinoma cells [152,153]. The metastatic niche plays a key role in determining whether the disseminated tumor cells should continue to proliferate, enter a dormant state or perish. The role of BMAs as important components of this metastatic niche

Figure 1. An overview of the roles of adipokines and adipocytes in the process of breast cancer bone metastasis. Various adipokines and adipocytes are involved in breast cancer development and progression to bone metastasis. Firstly, adipocytes can be subdivided into central and local adipocytes, and the former can affect breast cancer with altered adipokine secretion, especially in obese patients. Local adipocytes can be further subdivided into cancer-associated adipocytes (CAAs) in the breast and bone marrow adipocytes (BMAs) in the bone. Adipokines can be secreted by various kinds of cells: breast cancer cells secrete leptin, adiponectin, IL-1β, IL-8, IL-11, IGFBP2, IGFBP3, OSM, PTX3, VEGF, cathepsin K, angiopoietin-2, angiopoietin-like protein 2 and CCL2/MCP-1, which are involved in breast cancer bone metastasis; CAA secrete leptin, resistin, ATX, IL-6, TNF-α, IGF-1, HGF and IGFBP-2, which are involved in breast cancer progression; BMAs secrete leptin, adiponectin, IL-1β, IL-6, CXCL1, CXCL2, COX-2 and CCL2; bone stromal cells such as osteoclasts and osteoblasts secrete TGF-β, IL-6, MCP-1, VEGF, IL-1β and cathepsin K, which contribute to breast cancer bone metastasis. In addition, cancer-associated fibroblasts (CAFs) secrete CXCL12, CXCL14, IGF-1 and IGF-2.
has been suggested recently [79,117]. Since BMAs increase with age, their role as a metastatic niche can also increase among elderly breast cancer patients. The following are the mechanisms by which BMAs are involved in the bone metastasis of breast cancer.

6.1. Adipocytokines Secreted by BMA

BMAs secrete various adipocytokines, such as leptin, adiponectin, IL-1β, IL-6, VCAM-1, TNF-α and VEGF [113]. These adipocytokines affect cancer cell biology, and, for breast cancer, IL-1β overexpression in addition to leptin is reported to induce cancer cell colonization in BM [79]. Moreover, leptin reacts with leptin receptor (LepR) on BM stem cells to promote adipogenesis by activating the Jak2/STAT3 pathway [126,154]. Additionally, leptin secreted by BMAs reacts with LepR on tumor cells and contributes to tumor progression [155–157]. BMAs can secrete adiponectin, which in general takes part in tumor suppression [158], and tumor patients secrete more adiponectin [121]. However, some studies report that adiponectin promotes tumor growth and migration [34,159], and these differences may result from differences in adiponectin receptor isoforms [34]. BMAs secrete a large amount of IL-6 [160], which induces EMT in cancer cells through the JAK2/STAT3 pathway [161] and increases the metastatic potential of tumor cells by promoting tumor cell survival through the PI3K/AKT pathway [162]. An interesting point is that even if tumor cells do not express IL-6 receptor (IL-6R), the soluble form of IL-6R can activate IL-6 [163]. Therefore, if BMAs secrete both IL-6 and soluble IL-6R, they can contribute to the metastatic process. IL-6 also increases the number of BMAs and forms positive feedback [164]. CXCL1 and CXCL2 from BMAs are also involved in immune modulation, working as chemoattractants for macrophages, neutrophils and CD11b+Gr1+ cells [165,166]. These immune cells express CXCL2 receptors and suppress the anti-tumor immune response [167]. In addition, the COX-2/PGE2 signaling axis is involved in immune modulation, resulting in chronic inflammation and immune suppression in order to facilitate tumor evasion in the immune response [168]. COX-2 and PGE2 overexpression is a major cause of tumor-related bone degradation in bone metastasis [169,170]. The increase in COX-2 levels induced tumor colonization and osteoclastogenesis in a breast cancer mouse model, resulting in lytic bone metastasis [171]. CCL2 from adipocytes promotes cancer progression by increasing angiogenesis [172].

6.2. Lipid Transfer from BMAs to Breast Cancer Cells

BMAs are a source of lipids that enable solid cancer cells to undergo cancer cell proliferation, migration and invasion [79,173]. When breast cancer cells are cultured with adipocytes in a cell line study, lipid droplets accumulate within cancer cells, and expression levels of FABP4, CD36 and perilipin 2, molecules that play roles in lipid transfer, are increased. CD36 expression is increased when breast cancer cells are cultured with BMAs [173], and exogenous lipids are transferred to breast cancer cells by CD36 to promote the growth of cancer cells [174]. In an in vivo study, the number of BMAs was increased due to increased adipogenesis in the early phase of bone metastasis; however, the number of BMAs that had an ample amount of lipid droplets decreased as the tumor progressed, supporting the lipid transfer phenomenon from BMAs to tumor cells [175]. Bone metastasis occurs more frequently in rBMA-enriched regions (proximal femur, hip and lumbar spine) rather than in cBMA-enriched regions, because rBMAs tend to transform easily depending on their microenvironment, and thus they show a flexible response to metabolic interaction with tumor cells. In support of this, the loss of BMAs can be seen in bone metastasis.

7. Therapeutic Targets of Adipokines and BMAs for Bone Metastasis of Breast Cancer

Adipokines and BMAs play an important role in breast cancer bone metastasis through various pathways, and thus they can be effective treatment targets (Figure 2).
Figure 2. Candidates for targeted treatment of breast cancer bone metastasis through inhibition of adipokines and adipocytes. Adipokine and/or adipocyte inhibitors that have been reported to be effective in breast cancer bone metastasis treatment in preclinical and/or clinical studies are as follows: 1) SOST antibody (romosozumab) that suppresses BMA formation; 2) Ki16425 and Debio0719 secreted by CAAs that suppress ATX-LPA axis; 3) MLN1202, a monoclonal antibody to CCR2 secreted by BMAs; 4) anti-AREG antibody and IL-8 monoclonal antibody that suppress OSM secreted by breast cancer cells to inhibit osteolytic bone metastasis. Recombinant form IL-1 receptor antagonist (anakinra) that suppresses IL-1B secreted by breast cancer cells and BMAs or anti-IL-1B antibody (canakinumab) suppresses bone metastasis, as well as odanacatib (MK-0822) that suppresses cathepsin K from breast cancer cells and osteoclasts, also inhibit bone metastasis, along with L-235 (L-006235). Lastly, 1) 1D11, an anti-TGF-β antibody that represses TGF-β secretion secreted by bone stromal cells such as osteoblasts, 2) SD-208, a small molecule TβRI-I (SD-208), 3) small molecule TGF-β inhibitor (YR-290, and 4) LY2109761 all suppress breast cancer bone metastasis.

7.1. Adipokine Modulators

Adipokine modulators, namely CCL2–CCR2 axis inhibitors, can suppress cancer cells. MLN1202, a monoclonal antibody to CCR2, is currently being tested in a clinical trial for breast cancer bone metastasis [176]. Ki16425, a non-lipid competitive inhibitor of LPA1 and LAP3, decreased breast cancer bone metastasis in a mouse model [37], and Debio0719, the R-stereoisomer of Ki16425, decreased the lung and bone metastasis of breast cancer in a mouse model [177]. Cathepsin K inhibitors suppressed breast cancer-mediated osteolysis and breast cancer cell invasiveness [86], and odanacatib (MK-0822), one of the cathepsin K inhibitors, decreased bone turnover markers in a phase II clinical trial of breast cancer bone metastasis [178]. Another cathepsin K inhibitor, L-235 (L-006235), decreases breast cancer cell-induced osteolysis and tumor burden in the bone [85]. Various TGF-β inhibitors have been reported to suppress breast cancer bone metastasis. Firstly, when TGF-β type 1 receptor kinase inhibitor (TβRI-I) is transfected in the breast cancer cell line, both extensive bone metastasis and early bone metastasis are suppressed [179]. Secondly, anti-TGF-β antibody 1D11 suppresses bone loss and breast cancer bone metastasis [180], and SD-208, a small molecule TβRI-I, also suppresses breast cancer bone metastasis [181]. Other TGF-β inhibitors, YR-290 [182] and LY2109761 [183], have also been reported to suppress bone metastasis in breast cancer studies. Osteolytic bone metastasis was suppressed and survival was extended when IL-8 monoclonal antibody was injected into a mouse model using the
breast cancer cell line [48]. An important factor involved in oncostatin M (OSM)-induced osteolytic bone destruction is amphiregulin (AREG), and the anti-AREG antibody is reported to suppress OSM-induced osteoclastogenesis [69]. Anakinra, a recombinant form IL-1 receptor antagonist, or canakinumab, an anti-IL-1B IgG1 antibody, decreased bone metastasis in a mouse model study of breast cancer bone metastasis [184].

7.2. BMA Metabolism Inhibitors

A metabolic pathway can be a treatment target because there exists a metabolic interaction between BMAs and breast cancer cells. Fatty acid released from adipocytes as a result of lipolysis is transferred to cancer cells and produces energy through mitochondrial β oxidation. This process promotes tumor progression, and, thus, the suppression of fatty acid oxidation in cancer cells can be a treatment target. Trimetazidine, a fatty acid oxidation inhibitor, has been reported to induce cancer cell apoptosis [185], and malonyl-CoA decarboxylase (MCD) inhibitor suppresses fatty acid oxidation and hence decreases human breast cancer cell proliferation by increasing malonyl-CoA level, a key enzyme that blocks fatty acids from entering mitochondria [186]. There are two ways to suppress the transfer of fatty acids from adipocytes to tumor cells: 1) an inhibitor of fatty acid-binding protein 4 (FABP 4), which is a fatty acid transporter (BMS309403), can suppress cancer cell proliferation [187], and 2) blocking a transmembrane protein CD36 that is involved in fatty acid uptake with CD36-blocking antibody can decrease breast cancer cell metastasis [188,189].

7.3. BMA Inhibitors

Since BMAs play an important role in breast cancer bone metastasis, the suppression of BMA formation can be an effective way to suppress bone metastasis. Sclerotin (SOST) is originally secreted by osteocytes to suppress osteoblast differentiation and hence bone formation. SOST is also involved in adipocyte generation and metabolism [190,191]; the number and size of BMAs in long bones are actually decreased when inhibited by SOST [192]. Meanwhile, SOST expression is increased in breast cancer with bone metastasis, and the SOST antibody is reported to effectively suppress bone metastasis in breast cancer [193]. A monoclonal antibody to SOST, romosozumab, is being used for osteoporosis treatment in clinical practice, and further study is needed in order to implement its use in breast cancer patients with bone metastasis [194].

8. Conclusions

The role of adipokines and BMAs in breast cancer bone metastasis was explored in this review. Many different kinds of adipokines are secreted by various types of cells, and those that play an important role in the process of bone metastasis are secreted by breast cancer cells, CAAs, BMAs, osteoblasts and osteoclasts. Adipokines participate in bone metastasis through angiogenesis, cancer cell migration, EMT, osteoclastogenesis, osteolysis and escape from tumor dormancy. Besides secreting adipokines, BMAs also transfer lipids to breast cancer cells as a source of energy. Since adipokines and BMAs play an important role in the process of bone metastasis, adipokine and BMA inhibitors have potential as an effective target therapy in breast cancer bone metastasis, and a few preclinical and clinical studies have implicated their therapeutic effects. However, the diversity and complexity of adipokines and BMAs may cause unexpected side effects and bring about pro-tumor effects instead of the expected anti-tumor effect, for which we need to be prepared.

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