CURRENT CONCEPTS REVIEW

Newly Released Advances in the Molecular Mechanisms of Osseous Metastasis and Potential Therapeutic Strategies

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Abstract

The appearance of bone metastases (BM) in individuals with advanced solid cancers (breast, prostate, lung) often worsens their quality of life and prognosis. Although none have been fully effective, several strategies have been used to combat BM. Hence, the need for new data that could be useful for treating bone metastasis. To this end, we reviewed the recent literature on the subject. About patients with prostate cancer, treatments with PIP5K1α inhibitors have been found to inhibit tumor invasion and metastasis, and G protein-coupled receptor class C group 5 member A (GPRC5A) could be a future therapeutic target. Regarding patients with breast cancer, we found the following: Asperolide A could be another curative drug; targeting transforming growth factor-beta (TGFβ) and bone morphogenetic protein (BMP) signaling pathways, along with osteoclast activity, could be a favorable therapeutic approach in the preclusion of osteolytic bone destruction; TRAF6 inhibitors such as 6877002 appear promising; aiming the BMP4-SMAD7 signaling axis is an innovative therapeutic approach; there is favorable proof for the plausible therapeutic utilization of bone aiming immunostimulatory MOF (BT-isMOF) nanoparticles, and inhibition of IL4R and macrophages could have therapeutic benefits. For lung cancer, the function of LIGHT in osteolytic osseous illness instigated by metastatic non-small cell lung cancer should be highlighted.

Level of evidence: III

Keywords: Breast cancer, Bone, Lung cancer, Metastasis, Prostate cancer

Introduction

Bone metastases are a frequent complication of the most common human cancers (e.g., prostate, breast, lung). They are very painful and pose a risk of pathological fracture, and when associated with hypercalcemia, can be life-threatening for the patients with these metastases. Bone metastases can also cause renal failure, arrhythmias, and cardiac arrest.[1] Metastasis is the principal motive of cancer-related demise. The metastatic process involves the participation of tumor cells and tumor stromal cells to liberate metastatic cells into the blood circulation. Circulating tumor cells (CTCs) subsist circulatory cytotoxicity, extravasate, and colonize secondary locations, affecting the metastatic result.[2] In individuals with advanced solid cancers, such as breast, prostate, and lung cancer, the occurrence of bone metastasis negatively affects their quality of life and prognosis. In the first phase of the bone metastasis process, cancer cells affix to the endothelium in the bone marrow and endure in a dormant state by using hematopoietic niches present inside. Once the dormant stage is finished, cancer cells expand by interacting with diverse resident cells in the bone marrow, mainly osteoclasts and osteoblasts.[3] [Figure 1] summarizes the fundamental phenomena in the metastatic process. shows the two types of vicious cycles in the metastatic process: osteosclerotic and osteolytic [Figure 2].[1] This article will

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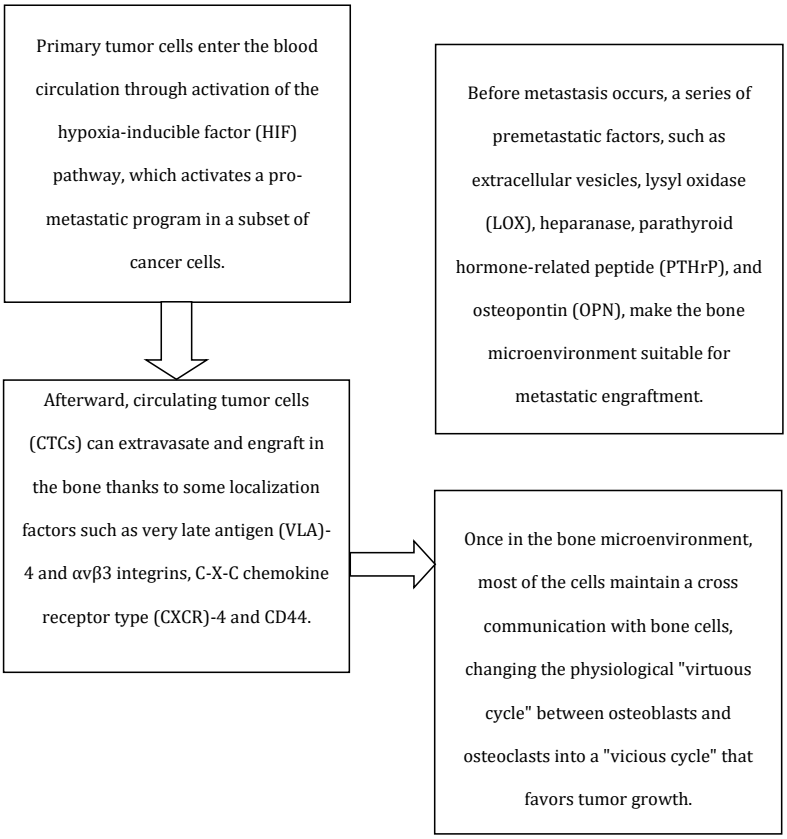


Figure 1. Summary of the fundamental phenomena that take place in the metastatic process.

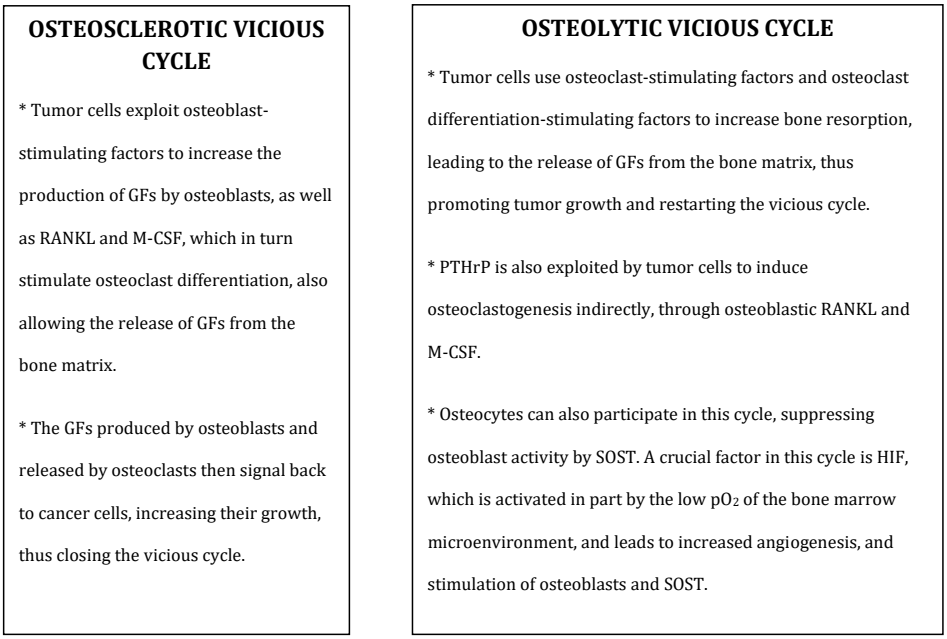


Figure 2. The two categories of vicious cicles in the metastatic process are osteosclerotic (usually used by prostate cancer cells) and osteolytic (a mechanism utilized by many types of tumors, including breast carcinoma). GFs, growth factors; RANKL, receptor activator of nuclear factor kappa B ligand; M-CSF, macrophage-colony-stimulating factor; PTHrP, parathyroid hormone-related protein; SOST, secretion of sclerostin; HIF, hypoxia-inducible factor; pO2, partial pressure (tension) of oxygen.

analyze some recent concepts on bone metastasis and metastasis of prostate cancer, breast cancer, and lung cancer [Table 1].

General Concepts of Bone Metastasis

The following issues of interest have been published concerning the general concepts of bone metastasis: a clinically actionable multidimensional mitogen-activated protein kinase (MAPK)7/matrix metalloproteinase (MMP)9 signaling hub in primary bone cancer metastasis; the appearance of cancer-associated fibroblasts as an essential cellular player in the bone metastasis process; the identification of small molecule inhibitors that diminish invasion and metastasis of aggressive cancers; that microRNA (miRNA)-128 modulates osseous neoplasms cells expansion and migration via the Wnt/beta-catenin and epithelial-mesenchymal transition (EMT) signal pathways; and that STAT3 phosphorylation at Ser727 and Tyr705 differentially rules the EMT-mesenchymal-epithelial transition (MET) switch and cancer metastasis.

Clinically actionable multidimensional MAPK7/MMP9 signaling center of activity in primary bone cancer metastasis

One study mentioned a multidimensional MAPK7/MMP9 signaling center of activity in primary bone cancer metastasis that might be clinically actionable. Reprogramming the transcriptomic landscape is a hallmark of metastasis; therefore, it is critical to detect

Table 1. Bone metastasis of cancer: topics analyzed in this article

THE METASTASIS PROCESS
GENERAL CONCEPTS
+Clinically actionable multidimensional mitogen-activated protein kinase 7/matrix metallopeptidase 9 (MAPK7/MMP9) signaling hub in primary bone cancer metastasis
+ Emergence of cancer-associated fibroblasts as an indispensable cellular player in the bone metastasis process
+ The identification of small molecule inhibitors that reduce invasion and metastasis of aggressive cancers
+ miRNA-128 modulates bone neoplasm cells' proliferation and migration through the WNT/beta-catenin and epithelial mesenchymal transition (EMT) signaling pathways
+ Signal transducer and activator of transcription 3 (STAT3) phosphorylation at Ser727 and Tyr705 differentially regulates the EMT/mesenchymal-epithelial transition (MET) switch and cancer metastasis
PROSTATE CANCER
+ Marker of dissemination to bones
+ Receptor tyrosine kinase-like orphan receptor 2 (ROR2) suppresses metastasis via regulation of the miR-199a-5p-PIAS3-AKT2 signaling axis
+ Caprylic acid (C8:0) promotes bone metastasis by dysregulated adipo-osteogenic balance in bone marrow
+ Prostate cancer cell-intrinsic interferon signaling regulates dormancy and metastatic outgrowth in bone
+ Establishment of tumor growth and metastasis is supported by bone marrow cells and is mediated by PIP5K1alpha lipid kinase
+ Ras and Wnt interaction contribute to bone metastasis
+ GPRC5A facilitates cell proliferation through cell cycle regulation and correlates with bone metastasis
+ Long noncoding RNA HOXA11-AS and transcription factor HOXB13 modulate the expression of bone metastasis-related genes
BREAST CANCER
Asperolide A prevents bone metastasis +
Osteolytic metastasis: prevention strategies +
Combined administration of a small-molecule inhibitor of TRAF6 and docetaxel diminishes skeletal metastasis and osteolysis +
Bioinformatic tool for exploring the molecular mechanisms of bone metastasis +
Development and characterization of a novel human 3D model of bone metastasis from breast carcinoma cultured in vitro +
Activation of canonical BMP4-SMAD7 signaling suppresses metastasis +
Arginine methylation-dependent LSD1 stability promotes invasion and metastasis +
Metal-organic framework nanoparticles for ameliorating breast cancer-associated osteolysis +
Causal Bayesian gene networks associated with bone, brain, and lung metastasis +
Monocyte-derived macrophages promote bone metastasis outgrowth +
MicroRNA-429 inhibits bone metastasis by regulating CrkL and MMP-9 +
Analysis of genomics and immune infiltration patterns of EMT related to breast cancer metastasizing to the bone +
Molecular insights into the interplay between adiposity, breast cancer, and bone metastasis +
LUNG CANCER
LIGHT/TNFSF14 promotes osteolytic bone metastases in patients with non-small cell lung cancer +
Serological molecular model for the early diagnosis and monitoring progression of bone metastasis +

the supporting master controllers driving pathological gene expression, especially in childhood cancers.[2] In a study by Green et al., whole tumors plus single-cell RNA-sequencing was used in primary bone cancer and CTCs to carry out a weighted analysis of the gene co-expression system. The aim was to discover organized changes in metastatic transcript expression systematically. Compared to information obtained from cell line models, clinical samples, and xenograft mouse models showed that MAPK7/MMP9 signaling is a driver of primary bone cancer metastasis. RNA interference knockdown of MAPK7 reduced expansion, colony creation, migration, tumor enlargement, macrophage residence/polarization, and lung metastasis. At the same time, there was a reduction in activated interleukins (ILs) IL-1B, IL-6, IL-8, and mesenchymal markers vimentin and vascular endothelial growth factor (VEGF) in response to MAPK7 loss.[2]

Cancer-associated fibroblasts (CAFs) could play various roles in cancer advancement and metastasis

Mukaida et al. have mentioned that cancer-associated fibroblasts (CAFs), which accumulate in cancerous tissues, could play various roles in cancer advancement and metastasis. Considering the existence of CAFs in areas of bone metastasis, they seem to play a role in this disease state. Therefore, it is crucial to understand the possible functions of CAFs in tumor advancement, specifically in bone metastasis. Activation of osteoclasts is a distinctive characteristic of bone metastasis. Therefore, drugs directed against osteoclast activation have often been used to treat it; unfortunately, they have not been effective in restraining the expansion of cancer cells in the bone marrow. Therefore, other types of resident cells, cancer-associated fibroblasts (CAFs), have been presumed to contribute to the growth of cancer cells in areas of bone metastasis.[3]

Small molecules of the PROAM02 class can be used to diminish cancer cell invasion and metastasis

A study has shown that small molecules of the PROAM02 class can reduce cancer cell invasion and metastasis. Transformed epithelial cells can turn on epithelial plasticity strategies and change from a sessile, epithelial phenotype to a motile, mesenchymal phenotype. This course of action is related to acquiring an invasive phenotype and the creation of remote metastases. The appearance of drugs that obstruct the procurement of an invasive phenotype or reverse the invasive mesenchymal phenotype to a more differentiated epithelial phenotype could be a favorable anticancer approach. In a high-throughput investigation based on E-cadherin (re) induction and restriction of tumor cell invasion, van de Merbel et al. screened 44,475 low molecular weight (LMW) compounds. The study identified some prospect compounds from the PROAM02 class. The chosen LMW compounds stimulated E-cadherin promoter action and restrained cancer cell penetration in many metastatic human cancer cell lines. Intraperitoneal use of chosen LMW compounds diminshed tumor burden in *in vivo* mouse prostate and breast cancer models. Furthermore, these LMW compounds reduced the intraperitoneal proliferation of xenografted human prostate cancer cells.[4]

miRNA-128 modulates osseous neoplasms cell growth and migration via the Wnt/beta-catenin and EMT signaling pathways

One publication determined a tumor-regulated role for microRNA (miR)-128 in osseous neoplasms by downregulation of the Wnt/β-catenin and EMT signaling pathways, which rendered a plausible goal for osseous neoplasm gene therapy. Although the function of miRNAs in inhibiting the growth and metastasis of osseous neoplasms has been studied, the possible supporting molecular mechanisms mediated by miR-128 causing the invasiveness of bone neoplasm cells are still not well comprehended. A study by Li et al. attempted to identify such mechanisms. It was observed that transfection of miR-128 avoided the propagation, migration, and incursion of osseous neoplasm cells. Genetic deletion of miR-128 in bone neoplastic cells avoided the activation of Wnt/β-catenin and EMT signaling pathways. Activation of Wnt or EMT avoided the proliferation and migration of miR-128-inhibited cells in osseous neoplasm cells. Exogenous introduction of miR-128 notably restrained tumor restoration in osseous neoplasm xenograft models.[5]

STAT3 phosphorylation at Ser727 and Tyr705 differentially controls the EMT-MET change and cancer metastasis

Signal transducer and activator of transcription 3 (STAT3) phosphorylation at tyrosine 705 and serine 727 have been shown to differentially regulate the EMT/MET switch in various CSC molecular subtypes to complete the metastatic process. EMT/MET processes have been suggested to be important in cancer metastasis. The study published by Lin et al. on metastasis in bone marrow-derived mesenchymal stem cell (BM-MSC)-driven lung cancer models shpwed that BM-MSC-induced signaling activated early propagation of CD133+/CD83+ cancer stem cells (CSCs) from primary slocations soon following STAT3 activation.[6]

[Table 2] summarizes the possible future pharmacological actions to be considered to fight cancer bone metastases.

Prostate cancer

According to Nastaly et al., prostate cancer is one of the most frequent cancers in male. Even though 5-year endurance in individuals with localized illness is almost 100%, metastatic illness endures irremediable [Figure 3].[7] According to Lin et al., prostate cancer causes more than 300,000 cancer deaths each year.[8]

Epidermal growth factor receptor (EGFR) overexpression (EGFRover) is a stable and EMT-independent marker of prostate cancers spreading to rigid organs, preferentially bones

According to Nastaly et al., markers indicating metastatic

Table 2. Possible future pharmacological actions to be considered in the fight against cancer bone metastases

Drugs affecting multidimensional mitogen-activated protein kinase 7/matrix metallopeptidase 9 (MAPK7/MMP9) signaling hub.
Drugs directed against the activation of cancer-associated fibroblasts (CAFs).
Drugs that block the acquisition of an invasive phenotype or that reverse the invasive mesenchymal phenotype into a more differentiated epithelial phenotype.
Drugs affecting the following processes: miR-128 transfection suppressing proliferation, migration and invasion of bone neoplastic cells; genetic deletion of miR-128 in bone neoplastic cells suppressing activation of the Wnt/β-catenin and epithelial-mesenchymal transition (EMT) signaling pathways; activation of Wnt or EMT blocking proliferation and migration of miR-128-inhibited cells in bone neoplastic cells; and exogenous introduction of miR-128 markedly inhibiting tumor regeneration in bone neoplasm xenograft models.
Drugs that influence the signal transducer and activator of transcription 3 (STAT3) phosphorylation at tyrosine 705 and serine 727 that differentially regulates the EMT/mesenchymal-epithelial transition (MET) switch in different molecular subtypes of cancer stem cells (CSC) to complete the metastatic process.

spread are needed. They studied epidermal growth factor receptor (EGFR) overexpression (EGFRover) was monitored in 1039 primary tumors, in circulating tumor cells from 39 d'Amico high-peril individuals, and in metastatic samples from 21 castration-resistant prostate cancer cases. EGFR status was compared with clinical data, and many molecular factors were evaluated by immunohistochemistry and gene ontology analysis.[7] The functional aspect of EGFR was assessed by plating prostate cancer (PC-3) cells on soft and rigid matrices. EGFRover was found in 14% of primary tumors, associated with poorer metastasis-free endurance and an independent predictor of poorer overall endurance.

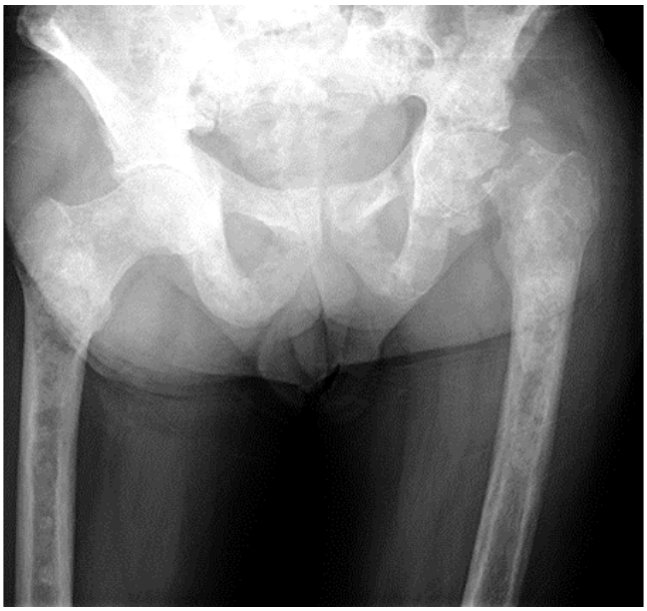


Figure 3. Bone metastasis in prostate cancer: Anteroposterior radiograph of the pelvis. Multiple metastatic involvements, blastic lesions, and pathologic hip fracture in a patient with advanced prostate cancer.

EGFRover was related to a pro-migratory and pro-metastatic phenotype of tumor cells and a content-rich in collagen fibers. All circulating tumor cells (found in 13% of individuals) were positive for EGFR, regardless of their EMT-related phenotype. EGFRover was more frequent in castration-resistant osseous metastases (29% of individuals) and favored the growth of human prostate cancer cells in rigid matrices imitating bone stiffness. Ultimately, EGFRover was found to be a stable and EMT-independent marker of prostate cancers spreading to rigid organs, preferentially bones.[7]

Receptor tyrosine kinase-like orphan receptor 2 (ROR2) suppresses metastasis via regulation of miR-199a-5p-PIAS3-AKT2 signaling axis

According to Tseng et al., tyrosine kinase-like receptor orphan receptor 2 (ROR2), a noncanonical Wnt receptor, has an important role in the formation of the skeleton, osteoblast differentiation, and bone creation.[9] In a study they published, they investigated the function of ROR2 in prostate cancer metastasis by analyzing online data sets from Oncomine and using immunohistochemical staining on a tissue array to establish the association between ROR2 expression level and illness result. A transwell assay and orthotopic xenograft model in nude mice was performed to explore how ROR2 rules the migration and invasion of prostate cancer cells. Then, a micro western array (MWA), a high-throughput Western blot platform, was applied to study the downstream signaling pathways ruled by ROR2. Compared with PZ-HPV-7 and RWPE-1 nonmalignant cells, prostate cancer cell lines expressed an inferiorlevel of ROR2 protein. Constitutive expression of ROR2 in PC-3, DU-145, or C4-2B PCa cells substantially avoided cell migration and invasion and EMT proteins. MWA, western blotting, and microRNA analysis demonstrated that upregulation of ROR2 avoided miR-199a-5p expression, increasing PIAS3 expression. PIAS3 upregulation then reduced protein kinase B (AKT)2 expression and AKT phosphorylation, inhibiting migration and invasion of prostate cancer cells *in vitro* and the orthotopic xenograft mice model. Immunohistochemical staining

of a tissue array and analysis of Oncomine data sets showed that ROR2 genes and proteins level was much inferior in metastatic prostate cancers than in primary cancers or adjacent normal prostate tissue. In patients with prostate cancer, low levels of ROR2 was related to poor endurance and an elevated recurrence rate. In conclusion, ROR2 was observed to suppress prostate cancer metastasis by way of regulation of the PIAS3-PI3K-AKT2 signaling axis.[9]

Caprylic acid (C8:0) exalts osseous metastasis of prostate malignancies by a dysregulated adipo-osteogenic equilibrium in bone marrow

According to Wang et al., prostate cancer remains the most frequent noncutaneous cancer in male. Moreover, bone is the most common location of prostate cancer metastasis, and up to 90% of individuals with advanced prostate cancer suffer from osseous metastasis.[10] Obesity-instigated modification of the bone marrow microenvironment is a fundamental mediator of prostate cancer bone tropism. Nevertheless, the specific molecular mechanisms by which obesity produces modifications in the bone marrow microenvironment resulting in osseous metastasis of prostate cancer are not yet well comprehended. Wang et al. demonstrated that an elevated-fat diet (EFD) causes dyslipidemia and modifications in the bone marrow of nude mice: an expansion of the zone and the amount of adipocytes and a decrease in the zone and the amount of osteoblasts. An EFD expedited the expression of cyclooxygenase 2 (COX2) and restrained osteoprotegerin (OPG) in the osseous microenvironment. The total free fatty acids and caprylic acid (C8:0) levels were substantially superior in prostate cancer individuals with osseous metastases. *In vitro*, caprylic acid (C8:0) expedited osseous mesenchymal stem cell (MSC)-derived adipocytic differentiation, COX2 expression, and prostaglandin E2 liberation, while osteoblastic differentiation and OPG expression decreased. C8:0-treated adipocytes expedited penetration and migration of prostate cancer cells. These conclusions insinuate that C8:0 expedits osseous metastasis of prostate cancer by dysregulating the adipo-osteogenic equilibrium of bone marrow.[10]

Prostate cancer cell-intrinsic interferon signaling rules dormancy and metastatic outgrowth in osseous tissue

According to Owen et al., the latency related to the occurrence of osseous metastases in castrate-resistant prostate malignancy is attributed to dormancy, a situation in which cancer cells persevere before the formation of an overt lesion.[11] Utilizing single-cell transcriptomics and *ex vivo* profiling, the crucial function of tumor-intrinsic immune signaling in the holding of cancer cell dormancy has been uncovered. It has been shown that disappearance of tumor-intrinsic type I interferon happens in proliferating prostate cancer cells in osseous tissue. This disappearance avoids tumor immunogenicity and therapeutic reaction and fosters activation of bone cells to drive cancer advancement. Reestablishment of tumor-intrinsic type I interferon signaling by histone deacetylase inhibition augmented tumor cell visibility, boosted long-run antitumor immunity, and obstructed cancer growth in osseous tissue. The most important data were validated in individuals, including disappearance of tumor-intrinsic interferon signaling and immunogenicity in osseous metastases compared with primary malignancies. This study explained why contemporary immunotherapeutics is unsuccessful in prostate cancer bone metastases and provided a new therapeutic approach to triumph over the ineffectiveness of immune-based treatments in solid malignancies.[11]

The setting up of tumor expansion and metastasis is seconded by bone marrow cells and is mediated by PIP5K1alpha lipid kinase

Cancer cells ease tumor expansion and metastasis by utilizing many signals from the cancer-associated microenvironment. Nonetheless, it is unknown whether prostate cancer cells can enlist and use bone marrow cells to grow and survive. Moreover, the regulatory mechanisms supporting the interactions between prostate cancer cells and bone marrow cells are still unclear.[12] In one report, Karlsson et al. isolated bone marrow cells that constituted chiefly CD11b and Gr1 antigen-positive populations from xenograft PC-3 tumor tissues from athymic nu/nu mice. They observed that tumor-infiltrating cells alone could not form tumor spheroids, even with superior quantities and longer period.

However, tumor-infiltrated and prostate cancer cells formed many tumor spheroids compared with prostate cancer cells alone. In addition, they used xenograft athymic nu/nu mice with metastatic osseous lesions. It was shown that prostate cancer cells could not endure and caused the production of colony-forming units (CFUs) in media utilized for hematopoietic cell CFU studies. On the other hand, PC-3M cells endured when bone-marrow cells existed, leading to CFUs. These data demonstrated that prostate cancer cells require bone-marrow cells to help their proliferation and endurance and create bone metastases in the host environment. It was shown that prostate cancer cells treated with either siRNA for PIP5K1α or its specific inhibitor, ISA-2011B, failed to endure and create tumor spheroids together with bone marrow cells. Since the high expression of PIP5K1α was particular to prostate cancer cells and was associated with induced expression of VEGF receptor 2 in prostate cancer cells, these data insinuate that cancer cells could utilize PIP5K1α-mediated receptor signaling to enlist growth factors and ligands from the bone marrow-derived cells. Therefore, this investigation proposed a new mechanism that allows prostate cancer cells to increase proliferative and invasive profits within their associated host microenvironment. Treatments with PIP5K1α inhibitors could inhibit not solely tumor penetration and metastasis but also reinforce the host immune system.[12]

Ras and Wnt interaction contribute to bone metastasis

According to Lin et al., in the late phase of prostate cancer advancement, bone marrow is the most metastatic location, constituting around 70% of metastatic cases of individuals with prostate cancer.[8] Nevertheless, the trait of the osteophilic property of prostate cancer is still obscure. Newly released investigations have mentioned that Wnt and Ras signaling pathways are critical in osseous metastasis and are involved in various cytological modifications; however, their interrelationship is poorly understood.[8]

GPRC5A promotes cell rapid growth via cell cycle regulation and correlates with osseous metastasis

The findings of a study by Sawada et al. indicate that G protein-coupled receptor class C group 5 member A (GPRC5A) could be a potential treatment objective and prognostic marker molecule in advancing prostate malignancy.[13] The prognosis of individuals with advanced hormone-refractory prostate cancer and/or bone metastases is poor. Therefore, multiple therapeutic targets have been investigated to augment the endurance of individuals with prostate cancer, including orphan GPRCs. Sawada et al. used integrative gene expression analysis of datasets recorded for prostate cancer cell lines, identifying GPRC5A as a potential therapeutic molecule. A Kaplan–Meier analysis of The Cancer Genome Atlas datasets showed that individuals with elevated GPRC5A expression had substantially shorter overall endurance. PC3 prostate cancer cells with CRISPR/Cas9-mediated GPRC5A knockout showed substantially low cell expansion both *in vitro* and *in vivo*. RNA-seq demonstrated that GPRC5A knockout PC3 cells had dysregulated expression of cell circle-related genes, resulting in cell circle detention at the G2/M stage. In addition, the registered gene expression profile data set demonstrated that the expression level of GPRC5A in the original lesions of patients with prostate malignancy who had bone metastases was superior than that of patients without bone metastases. PC3 GPRC5A knockout cells failed to create osseous metastases in xenograft mouse models. Furthermore, the clinical study showed that GPRC5A expression levels in samples of patients with prostate cancer were correlated with osseous metastasis and the individual's Gleason score (GS). The mixed evaluation with immunoreactivity of GPRC5A and GS showed superior specificity for fortelling the eventuality of osseous metastases.[13]

Long noncoding RNA HOXA11-AS and transcription factor HOXB13 regulate the expression of osseous metastasis-related genes

The study results by Misawa et al. suggest that HOXA11-AS and HOXB13 of prostate cancer foment metastasis by regulating CCL2/CCR2 cytokine and integrin signaling in autocrine, paracrine manners (14). Long noncoding RNAs (lncRNAs) are currently considered essential regulators of gene expression that have an essential role in cancer appearance. Mosawa et al. encountered that homeobox A11 antisense RNA (HOXA11-AS), a strongly expressed lncRNA in cell lines arisen from prostate malignancy osseous metastases, facilitated cell penetration and proliferation of PC3 prostate cancer cells. Transcription factor homeobox B13 (HOXB13) was recognized as an upstream regulator of HOXA11-AS. HOXA11-AS regulated osseous metastasis-associated C-C motif chemokine ligand 2 (CCL2)/C-C chemokine receptor type 2 (CCR2) signaling in both PC3 prostate malignancy cells and SaOS2 osteoblastic cells. The HOXB13/HOXA11-AS axis also ruled integrin subunits (ITGAV and ITGB1) specific for prostate cancer osseous metastasis. HOXB13, together with HOXA11-AS, directly ruled the integrin-binding sialoprotein (IBSP) promoter. Conditioned medium comprising HOXA11-AS liberated by PC3 cells induced the expression of CCL2 and IBSP in SaOS2 osteoblastic cells.[14]

[Table 3] presents possible future therapeutic targets for treating prostate cancer metastases.

Table 3. Possible future therapeutic targets in the treatment of prostate cancer metastases

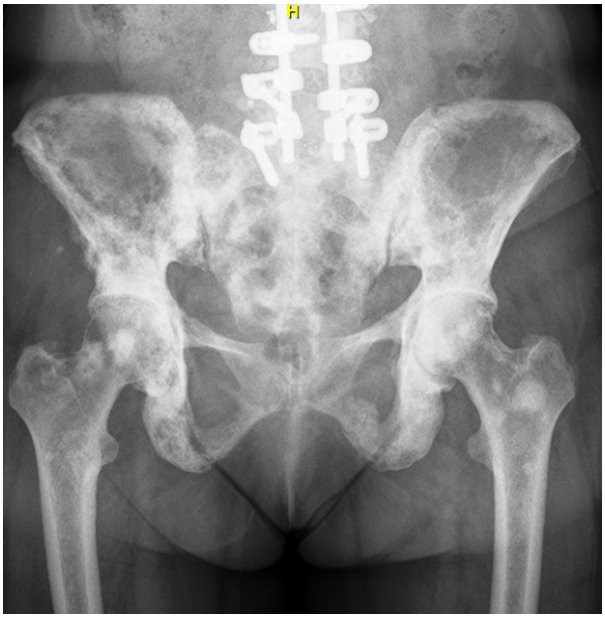
Epidermal growth factor receptor overexpression ($EGFR^{over}$) is a stable and independent marker of epithelial-mesenchymal transition (EMT) of prostate cancers disseminating to rigid organs, preferentially bones.
Tyrosine kinase-like orphan receptor 2 (ROR2) suppresses metastasis of prostate cancer via regulation of the PIAS3-PI3K-AKT2 signaling axis.
Caprylic acid (C8:0) promotes bone metastasis of prostate cancer by dysregulated adipo-osteogenic balance of bone marrow.
The restoration of tumor-intrinsic type I interferon signaling by histone deacetylase (HDAC) inhibition increased the visibility of tumor cells, promoted long-term antitumor immunity and blocked cancer growth in bone.
Treatments with PIP5K1α inhibitors could not only inhibit tumor invasion and metastasis, but also improve the host immune system.
Wnt and Ras signaling pathways are fundamental in bone metastasis and are involved in different cytological changes, although their interrelationship is not known.
G Protein-Coupled Receptor Class C Group 5 Member A (GPRC5A) is a potential therapeutic molecule
Homeobox A11 antisense RNA (HOXA11-AS), a lncRNA highly expressed in cell lines derived from prostate cancer bone metastases, promotes invasion and cell proliferation of PC3 prostate cancer cells.

Breast cancer

According to Jiang et al., breast cancer is the main cause of demise worldwide among female with malignant tumors, and osseus metastasis is the chief factor influcncing the prognosis of the disease [Figure 4]. Therefore, there is a need to develop antitumor and anti-breast-cancer-induced osteolytic drugs.[15]

Asperolide A prevents bone metastasis

A study by Jiang et al. studied the impact of asperolide A, a marine-derived drug, on osteolysis and receptor activator of nuclear factor kappa-B ligand (RANKL)-induced phosphoinositide 3-kinase (PI3K)/AKT/mechanistic goal of rapamycin (mTOR)/c-FOS/nuclear factor-activated T cell 1 (NFATc1) pathway activation, F-actin ring creation, and reactive oxygen species production *in vitro.*[15] The effect of asperolide A on MDA-MB-231 and MDA-MB-436 breast cancer cells *in vitro* was evaluated by CCK8 test, wound healing assay, transwell test, annexin V-fluorescein isothiocyanate/propidium iodide staining for cell apoptosis, and cell cycle assay. In addition, the impact of asperolide A was evaluated *in vivo*



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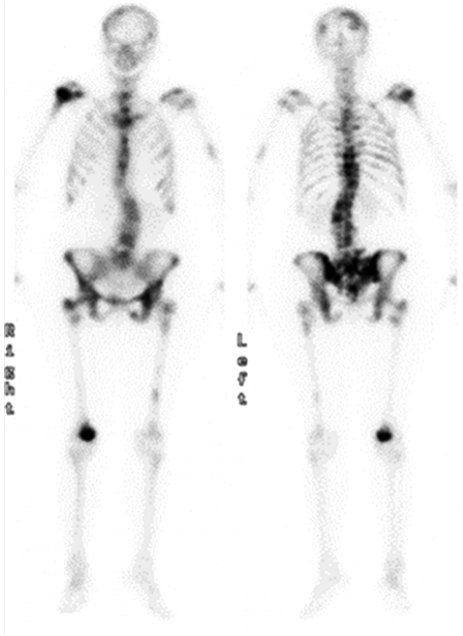

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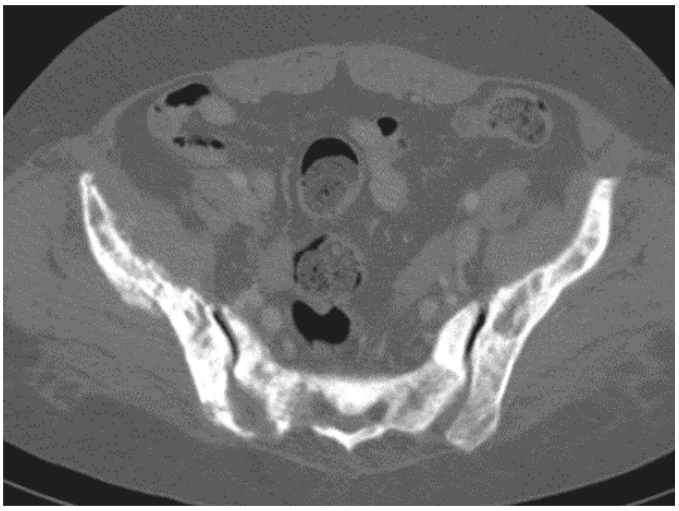


(c)

Figure 4 (a-c). Bone metastasis in breast cancer: Anteroposterior radiograph of the pelvis (a). Mixed metastatic lesions, blastic and lytic, are seen in a patient with disseminated breast cancer. Bone scan of the entire skeleton with multiple pathologic uptakes (b). Computed tomography (CT) image showing the metastatic lesions and pathologic fracture of the iliac bone (c).

utilizing a breast cancer-induced bone osteolysis nude mouse model, followed by microcomputed tomography, tartrate-resistant acid phosphatase staining, and hematoxylin and eosin staining. Asperolide A restrained osteoclast creation and differentiation, F-actin belt creation, reactive oxygen species activity, osteoclast-specific gene, and protein expressions, preventing PI3K/AKT/mTOR/c-FOS/NFATc1 signaling activation in a dose-dependent manner *in vitro*. Asperolide A also restrained breast cancer proliferation and cancer-induced bone osteolysis by diminishing osteoclast creation and function and inactivating PI3K/AKT/mTOR signaling *in vivo*. This data showed that asperolide A avoided metastatic breast cancer in the bone, indicating that asperolide A could be an innovative therapeutic medication for individuals with breast cancer who have osseous metastasis.[15]

Osteolytic metastasis: prevention strategies

Mandal et al. have stated that breast cancer is the most frequent cancer in females worldwide and that individuals who are diagnosed promptly tend to have a better prognosis and more prolonged survival.[16] Advanced phase breast malignancy frequently creates osteolytic metastases resulting in osseous destruction. Eeven though there are medications to manage osseous metastatic illness, their success has thus far been limited. In a recent article, Mandal et al. reviewed the mechanisms of osseous remodeling and osteolytic osseous metastases in breast malignancy. They also explored the potential of new natural and synthetic therapies in effectively preventing breast cancer-induced osteolysis and osteolytic breast cancer metastases.[16] According to Mandal, targeting transforming growth factor-beta (TGFβ) and bone morphogenetic protein (BMP) signaling pathways, together with osteoclast activity, seemss to be a favorable therapeutic approach for the preclusion of breast cancer-induced osteolytic osseous destruction and metastatic growth in metastatic bone niches. Initial investigations in animals insinuate that several natural and synthetic compounds and monoclonal antibodies prevent breast cancer-stimulated osteolytic activity. Nevertheless, to create efficacious treatments against breast cancer-induced osteolytic osseous illness, comprehensive preclinical investigations are still required to prove the pharmacokinetics and pharmacodynamics of these drugs and to understand the molecular mechanism(s) by which these molecules have anti-tumor growth and anti-osteolytic activity.[16]

Mixed utilization of a small-molecule inhibitor of TRAF6 and Docetaxel redues bone metastasis and osteolysis

Tumor necrosis factor receptor-associated factor 6 (TRAF6) has been involved in breast malignancy and osteoclastic osseous destruction. A study by Bishop et al. reported that 6877002, a proven small-molecule inhibitor of TRAF6, diminished metastasis, osteolysis, and osteoclastogenesis in osteotropic human and mouse breast malignancy models.[17] They found TRAF6 to be highly expressed in osteotropic breast malignancy cells, and its expression level was superior in individuals with osseous metastasis. Pre-exposure of osteoclasts and osteoblasts to noncytotoxic concentrations of 6877002 restrained cytokine-induced nuclear factor kappa B activation and osteoclastogenesis and diminished the capacity of osteotropic human MDA-MB-231 and mouse 4T1 breast malignancy cells to support bone cell activity. Besides, 6877002 restrained human MDA-MB-231-induced osteolysis in the mouse calvaria organ system and diminished soft tissue and osseous metastases in immunocompetent mice after intracardiac injection of mouse 4T1-Luc2 cells. It is important to emphasize that that mixed administration of 6877002 with docetaxel diminished metastasis and restrained osteolytic osseous damage in mice bearing 4T1-Luc2 cells. Therefore, TRAF6 inhibitors such as 6877002 (in solitude or in association with customary chemotherapy) appear promising for treating metastatic breast malignancy.[17]

Bioinformatics instrument for studying the molecular mechanisms of osseous metastasis

Advanced breast malignancy often results in bone metastasis; nonetheless, the molecular mechanisms underlying the attraction of breast cancer cells for bone remain obscure. Liu et al. created nomograms based on a competing endogenous RNA (ceRNA) network. They analyzed tumor-infiltrating immune cells to clarify molecular pathways to foretell prognosis in individuals with breast malignancy.[18] This study attained the RNA expression profile of 1091 primary breast cancer samples included in The Cancer Genome Atlas database, 58 from individuals with osseous metastases. The differential RNA expression patterns between breast cancer with and without bone metastasis were analyzed, and a ceRNA network was developed. Cibersort was used to discriminate immune cell types based on tumor transcripts. Nomograms were then defined based on the ceRNA network and immune cell analysis. The value of the prognostic factors was assessed by Kaplan–Meier survival analysis and Cox proportional hazard model. Significant differences in lncRNAs, 18 miRNAs, and 20 messenger RNAs were found between breast cancer with and without bone metastasis, which was used to construct a ceRNA network. A Kaplan–Meier analysis showed that the protein-coding genes GJB3, CAMMV, PTPRZ1, and FBN3 were significantly differentially expressed. Substantial dissimilarities in the copiousness of plasma cell and follicular helper T cell populations were also observed between the two groups. Besides, the ratio of mast cells, gamma delta T cells, and plasma cells were different according to illness location and phase. This study demonstrated that an elevated ratio of follicular helper T cells and a low ratio of eosinophils promote endurance and that DLX6-AS1, Wnt6, and GABBR2 expression could be associated with osseous metastasis in breast malignancy.[18]

Development and characterization of a newly released human 3D model of osseous metastasis from breast cancer cultured in vitro

Salamann et al. have created a newly released human 3D model of osseous metastasis from breast cancer utilizing

fresh tissue from human vertebral bone metastases from patients with breast cancer capable of retaining the tumor microenvironment.[19] The tissue model was based on *ex vivo* culture for up to 40 days, with constant monitoring of tissue viability, gene expression profile (IL-10, IL-1b, MMP1, MMP7, parathyroid hormone (PTH)1R, PTH2R, tumor necrosis factor, ACP5, SPI1, VEGF-A, cathepsin K, TGF-β) and histological and immunohistochemical analyses (E-cadherin, N-cadherin, cytokeratin 8, cytokeratin 18, Ki67, caspase 3, estrogen receptor alpha, CD68, and CD8). The findings proved that such an advanced breast cancer bone metastasis model was reliable, reproducible, and cost-effective and was able to retain and sustain long-run tissue viability and show molecular markers, tissue histomorphology, tissue micro-architecture, and antigen expression. This investigation provided for the first time the viability and underlying reason for the use of an advanced human-derived alternative model for cancer research and testing of innovative medications and approaches, bearing in mind individual patient characteristics and specific tumor subtypes to predict patient-specific reactions.[19]

Initialization of canonical BMP4-SMAD7 signaling silences metastasis

Eckhardt et al. have shown that BMP4 blocks metastasis in animal models of breast carcinoma and foretells more prolonged endurance in individuals.[20] BMP4 acted as an autocrine mediator in preclinical models of spontaneous metastasis to modulate several genes known to regulate metastasis, including SMAD7, through the activation of canonical BMP-SMAD signaling. Reestablished BMP4 expression, or treatment with BMP4 protein, obstructed metastasis and augmented endurance by sensitizing cancer cells to anoikis, diminishing the amount of circulating tumor cells. Gene silencing of BMP4 or its downstream mediator, SMAD7, inverted this phenotype. The use of recombinant BMP4 notably diminished spontaneous metastasis to lung and osseous tissue. Raised BMP4 and SMAD7 foretold longer relapse-free endurance and overall endurance in individuals with breast carcinoma; this indicates the relevance of canonical BMP4 signaling in the suppression of metastasis and highlights new ways for treatment against metastatic disease. Targeting the BMP4-SMAD7 signaling axis is a newly released therapeutic approach to fight metastatic breast carcinoma, a condition in which no reduction in mortality of the patients has been achieved over the past 20 years.[20]

Arginine methylation-dependent LSD1 stability expedites penetration and metastasis

According to Liu et al., histone lysine-specific demethylase 1 (LSD1), the first recognized histone demethylase, is overexpressed in many tumor types, including breast carcinoma. Nevertheless, the mechanisms causing LSD1 dysregulation in breast carcinona undure obscure.[21] In their study, Li et al. observed that protein arginine methyltransferase 4 (or CARM1) demethylates LSD1 at R838, which expedites the copling of deubiquitinase USP7, leading to the deubiquitination and stabilization of LSD1. Furthermore, CARM1- and USP7-dependent LSD1 stabilization played a crucial function in the repression of E-cadherin and the activation of vimentin transcription via promoter H3K4me2 and H3K9me2 demethylation, apiece, events that promote penetration and metastasis of breast carcinoma cells. In human malignant breast carcinoma samples, LSD1 arginine methylation levels correlated consistently with tumor grade. These findings revealed a sole mechanism governing LSD1 stability by arginine methylation, emphasizing the function of the CARM1-USP7-LSD1 axis in breast carcinoma advancement.[21]

Metal-organic structure nanoparticles for improving breast carcinoma-associated osteolysis

A study published by Pang et al. has pointed out the potential therapeutic application of BT-immunostimulatory metal-organic structure (isMOS) nanoparticles in treating breast carcinoma bone metastases.[22] In their study, their authors functionalized immunostimulatory cytosine-phosphate-guanosine-loaded metal-organic framework nanoparticles with bone targeting capabilities by surface modification with zoledronic acid. The functionalized BT-isMOF nanoparticles were observed to bind strongly to calcium phosphate *in vitro* and accumulate in osseous tissues *in vivo*. *In vitro* cellular and biochemical studies showed that BT-isMOS nanoparticles could probably restrain osteoclast creation while inducing macrophage polarization toward the M1 pro-inflammatory phenotype. Besides, utilizing the intratibial murine model of breast carcinama osseous metastasis, they demonstrateded that use of BT-isMOS nanoparticles substantially avoided osteoclast-mediated osseous destruction and increased the polarization of tumor-resident macrophages toward the M1 phenotype.[22]

Causal Bayesian gene systems associated with bone, brain, and lung metastasis

Using a machine learning strategy, a study published by Park et al. attempted to determin sole causal systems of genes associated with bone, brain, and lung metastasis of breast carcinoma.[23] Bayesian network analysis recognized differentially expressed genes in primary breast carcinoma tissues, bone, brain, and metastatic lung tissues, and the clinicopathological characteristics of individuals attained from Gene Expression Omnibus microarray datasets. Bayesian causal networks of breast metastasis to remote locations (bone, brain, or lung) were evaluated by measuring how well each specific breast cancer metastasis fit the data, comparing the structures with known experimental evidence, and reporting the predictive results capabilities of the structures. It was reported for the first time that molecular genetic signatures are specific for different types of breast carcinoma metastasis. Several genes, including CHPF, ARC, ANGPTL4, NR2E1, SH2D1A, CTSW, POLR2J4, SPTLC1, ILK, ALDH3B1, PDE6A, SCTR, ADM, HEY1, KCNF1, and UVRAG, were encountered to be diviners of breast carcinoma-specific metastasis risk. POLR2JA, SPTLC1, ILK, ALDH3B1, and estrogen receptor expression were substantially releted to breast carcinoma osseous

metastasis. PDE6A and NR2E1 expression was causally related to breast carcinoma brain metastasis. The expression of HEY1, KCNF1, UVRAG, and estrogen and progesterone receptors were markedly related to breast carcinoma lung metastasis. The causal Bayesian network structures of these genes allow us to determine possible interactions between genes in the remote metastasis of breast carcinoma, including bone, brain, and lung. They could be conceivable candidates for the management of breast carcinoma metastasis.[23]

Macrophages coming from monocytes promote osseous metastasis outgrowth

Ma et al. have mentioned that macrophages, as an essential ingredient of the tumor microenvironment, promote tumor advencement and metastasis.[24] Their investigation encountered that macrophages are ample in breast carcinoma osseous metastases in humans and mice. Ablation of macrophages significantly inhibited the growth of bone metastases. Lineage tracking experiments suggested that these macrophages are derived mainly from Ly6C+CCR2+ inflammatory monocytes. Ablation of the chemokine receptor, CCR2, substantially restrained osseous metastasis growth and prolonged endurance. Immunophenotyping recognized that osseous metastasis-associated macrophages express elevated levels of CD204 and IL-4R. Moreover, monocyte/macrophage-restricted IL-4R ablation substantially restrained osseous metastasis growth, and IL-4R null mutant monocytes failed to promote osseous metastasis outgrowth. This investigation detected a subset of monocyte-derived macrophages that promote breast cancer osseous metastasis in an IL-4R-dependent manner, suggesting that inhibition of IL-4R and macrophages could have potential therapeutic benefits against breast carcinoma osseous disease.[24]

MicroRNA-429 restrains osseous metastasis by ruling CrkL and MMP9

According to Zhang et al, many miRNAs have been validated in metastatic breast carcinoma, such as the miR200 family.[25] Zhang et al. stated that previous studies had recognized microRNA-429 (miR-429) as a regulatory molecule for breast carcinoma osseous metastasis. Nevertheless, the repercussions of miR-429 and its regulatory axis on the bone microenvironment of metastatic breast cancer had not been studied in depth. Their study found a positive relationship between miR-429 expression in clinical tissues and osseous metastasis-free interlude. A negative relationshipwas found between miR-429 expression and the grade of osseous metastasis. MDA-MB-231 cells with bone metastases were cultured, and a conditioned medium was used to discover the impact of miR-429 on osteoblasts and osteoclasts *in vitro*. An orthotopic osseous destruction model and a left ventricle implantation model were constructed to investigate the impact of miR-429 on the metastatic bone environment *in vivo*. The transfection experiments demonstrated that the expression levels of V-crk sarcoma virus CT10 oncogene homolog-like (CrkL) and MMP9 were negatively regulated by miR-429. The *in vitro* co-culture studies demonstrated that miR-429 fostered osteoblast differentiation and CrkL fostered osteoclast differentiation. The two animal exoeriments demonstrated that miR-429 decreased local osseous destruction and remote osseous metastasis, but CrkL potentiated these impacts. Moreover, CrkL and MMP9 expression at the same time reduced as a consequence of augmented miR-429 expression. These results further demonstrate the potential mechanism and impact of the miR-429/CrkL/MMP9 regulatory axis on the osseous microenvironment in breast carcinoma osseous metastasis.[25]

Study of genomics and immune infiltration arrangements of epithelial-mesenchymal transition-related to breast carcinoma metastasizing to osseous tissue

A study by Liu et al. attempted to arrange a weighted coexpression network and breast carcinoma prognosis assessment system utilizing genome-wide specific expression profiling mixed with EMT-related genes; they aimed to evaluate the prognostic risk of the spread of metastatic breast carcinoma to the osseous tissue.[26] Four gene expression datasets of many samples from Gene Expression Omnibus (GEO) were downloaded and mixed with the dbEMT database to screen out EMT differentially expressed genes (DEGs). Utilizing the GSE20685 dataset as a training set, a weighted coexpression network was designed for EMT DEGs, and the most relevant core genes for metastasis were chosen. Eight core genes were chosen to build prognostic evaluation models to calculate survival rates at 3, 5, and 10 years. Univariate and multivariate Cox regression analyses assessed the independent foretelling ability of the models. Two GEO datasets related to breast cancer osseous metastases were downloaded and utilized to carry out differential genetic studies. CIBERSORT was utilized to differentiate 22 immune cell types based on tumor transcripts. Differential expression study demonstrated a total of 304 DEGs that were chiefly related to proteoglycans in cancer, PI3K/AKT and TGF-β signaling pathways, mesenchyme formation, focal adhesion, and cytokine coupling functionally. The 50 core genes were chosen, and a linear peril evaluation model related to survival was constructed, consisting of eight genes (FERMT2, ITGA5, ITGB1, MCAM, CEMIP, HGF, TGFBR1, F2RL2). The survival percentage of elevated-peril cohort individuals was much inferior than that of the low-peril cohort, and the 3-, 5-, and 10-year areas under the curve were 0.68, 0.687, and 0.672, apiece. Besides, DEGs of breast cancer osseous metastases were explored, and BMP2, BMPR2, and GREM1 were differentially expressed in both datasets. In GSE20685, memory B cells, resting memory T cell CD4 cells, T regulatory cells, γδ T cells, monocytes, M0 macrophages, M2 macrophages, resting dendritic cells, resting mast cells, and neutrophils showed a signiiicantly different allocation between the elevated- and low-peril cohorts. In GSE45255, there was a substantial dissimilarity in the profusion of activated natural killer cells, monocytes, M0 macrophages, M2 macrophages, resting dendritic cells, and neutrophils in the high- and

low-risk groups. Based on the weighted coexpression network for breast cancer and metastasis-related DEGs, core genes were examined to study a prognostic model and immune infiltration patterns of metastatic breast cancer. The findings of this research procured a real basis to bioinformatically examine the molecular mechanisms of metastatic breast cancer spread to the osseous tissue and the likelihood of foretelling patient survival.[26]

Molecular visions into the interaction between adiposity, breast cancer, and osseous metastasis

According to Soni et al., cancer is an intricate illness in which several pre-existing diseases enhance its pathology.[27] In cancer, the extracellular environment has several intrinsic physiological factors whose levels are modified with aging and preexisting diseases. In fatness, the tumor microenvironment and metastases are improved with factors coming from the local environment and other physiological compartments. In the same way, in fatness, the environment of cancer cells, both at the location of origin and the secondary location, i.e., the metastatic niche, has substantially more phenotypically-altered adipocytes than that of nonobese patients with cancer. In fact, fatness has been connected to cancer advancement, metastasis, and impedance to treatment. Adipocytes dovetail with tumor cells and neighboring stromal cells from primary and metastatic locations.[27] Soni et al highlighted the relevance of bidirectional interplays between adipocytes and breast tumor cells in breast cancer advancement and its osseous metastases. This article described the function of several adipocyte-derived factors in tumor growth and mentioned the importance of adipocyte-derived bone metastatic factors in the appearance of breast cancer osseous metastasis. The authors provided molecular insight into the interaction between adipocytes and tumor cells implicated in breast cancer osseous metastasis. Nonetheless, further investigations are required to establish whether targeting cancer-associated adipocytes is a promising therapeutic approach for treating breast carcinoma osseous metastasis.[27]

[Table 4] summarizes the most critical data from the recent literature on breast cancer bone metastasis.

Lung cancer

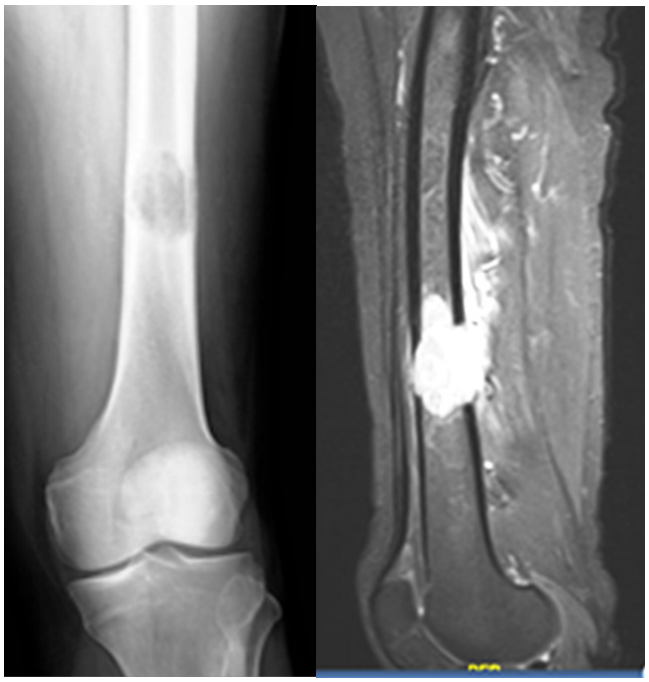
The forecast is very bad for lung cancer and osseous metastasis [Figures 5; 6].[28]

LIGHT/TNFSF14 expedites osteolytic osseous metastases in patients with non-small cell lung carcinoma

A publication by Brunetti et al. has stated that tumor necrosis factor superfamily member 14 (TNFSF14, or LIGHT) promotes osteolytic osseous metastases in individuals with non-small cell lung cancer (NSCLC).[29] Therefore, LIGHT could be a new therapeutic objective in osteolytic osseous metastases. LIGHT, a component of the cytokine network, regulates innate and adaptive immune responses that expedite the homeostasis of lymphoid organs, liver, and osseous tissue. Metastatic tumors frequently alter the tissue microenvironment, which alters the homeostasis of the infiltrated organ; nevertheless, the underlying mechanisms are not fully understood. In their report, Brunetti et al. studied the function of LIGHT in osteolytic osseous disease caused by metastatic NSCLC. Individuals diagnosed with NSCLC osseous metastasis demonstrated substantially more elevated levels of LIGHT expressed in monocytes than in nonmetastatic tumors and healthy controls. Serum LIGHT levels were also more elevated in individuals with osseous metastases than in controls, insinuating a function for LIGHT in the stimulation of osteoclast precursors. Increased RNA expression and serum levels of RANKL were also found in individuals with osseous metastases, whereby the addition of anti-LIGHT or RANK-fragment crystallizable region in peripheral blood mononuclear cell cultures resulted in significant inhibition of osteoclastogenesis. The mouse lung cancer cell line LLC-1 was used to model this finding in mice. Follwoing intratibial implantation, wild-type mice

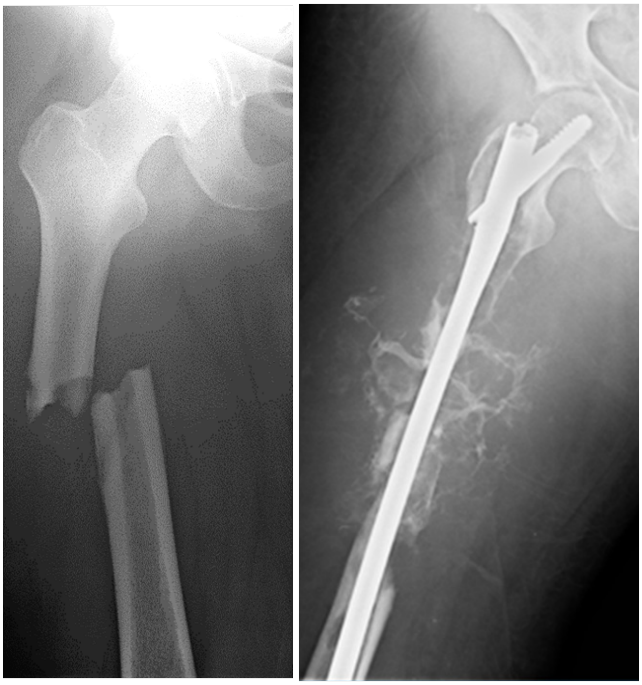
Table 4. Most important data from recent literature on breast cancer bone metastasis

Asperolide A appears to be a potential novel curative drug candidate for patients with breast cancer and bone metastases.
Targeting transforming growth factor beta (TGFβ) and bone morphogenetic protein (BMP) signaling pathways along with osteoclast activity appears to be a promising therapeutic strategy in the prevention of breast cancer-induced osteolytic bone destruction and metastatic growth in bone metastatic niches.
A verified small-molecule inhibitor of TRAF6, 6877002, reduced metastasis, osteolysis and osteoclastogenesis in osteotropic human and mouse models of breast cancer
To explore the molecular mechanisms of bone metastasis in patients with breast cancer, a bioinformatics tool was developed and factors that can predict the occurrence of bone metastasis were identified.
Targeting the BMP4-SMAD7 signaling axis is a novel therapeutic strategy to combat metastatic breast cancer.
Bone targeting immunostimulatory MOF (BT-isMOF) nanoparticles.
Inhibition of interleukin-4R and macrophages could have potential therapeutic benefit against breast cancer bone disease.



(a) (b)

Figure 5 (a-b). Bone metastasis in lung cancer: Patient presenting for consultation due to pain of weeks of evolution and functional impotence for walking. (a) X-ray showing a lytic lesion at risk of fracture in the femoral diaphysis. After the study, lung cancer with bone metastasis was diagnosed. Magnetic resonance imaging (MRI), sagittal view, showing a bone lesion with rupture of the posterior cortex and soft tissue mass (b).



(a) (b)

Figure 6 (a-b). Bone metastasis in lung cancer: Patient with lung cancer presented clinically with pathological fracture of the femur after minimal trauma. The radiograph shows a lytic image at the bony ends of the fracture site (a). Radiological image 6 months later. Tumor progression (b).

demonstrated a more elevated amount of osteoclasts but a lower number of osteoblasts and less osteoid creation. Inversely, TNFSF14-/- mice did not show a substantial loss of bone tissue or other variations in bone homeostasis associated with this model. This infomation denote that LIGHT is a crucial control mechanism for regulating bone homeostasis in the course metastatic penetration.[29]

Serological molecular model for the prompt determination and advancement monitoring of osseous metastasis

Teng et al. have attempted to design a new model for prompt recognition of individuals with lung cancer at risk of osseous metastasis.[28] In that study, 205 individuals with primary lung cancer were enrolled as a test group, of which 127 individuals had osseous metastasis; the other 78 individuals without osseous metastasis were set as negative controls. In addition, 106 healthy volunteers were included as normal controls. Serum levels of diverse bone microenvironment cytokines (CaN, OPG, PTHrP, and IL-6) and bone turnover markers (tP1NP, β-CTx) were found in all samples by ECLIA or ELISA assay. Receiver operating characteristic (ROC) curves and multivariate analyses were carried out to assess the diagnostic ability and evaluate the attributable risk of osseous metastasis for each marker; the diagnostic model was determined by logistic regression analysis. The prospective validation cohort consisted of 44 individuals with stage IV primary lung carcinoma followed for at least two years. During that time, serum concentrations of biochemical bone markers were studied. The serological molecular model for diagnosing osseous metastasis was logit (p). The ROC analysis demonstrated that when logit (p) > 0.452, the area under the curve was 0.939 (sensitivity: 85.8%, specificity: 89.7%). Model validation showed accuracy with an elevated grade of consistency (specificity: 85.7%, specificity: 87.5%, Kappa: 0.770). The mean prediction time of the appearance of osseous metastases of the model was 9.46 months earlier than that of diagnosis by bone scintigraphy. Serum OPG, PTHrP, tP1NP, β-CTx, and the diagnostic model logit (p) were all positively correlated with osseous metastasis advancement. This diagnostic model appears to be an uncomplicated, non-invasive, and sensitive instrument for detecting the appearance and monitoring the advancement of osseous metastases in individuals with lung carcinoma.[28]

Metastasis is the leading cause of cancer-related death. In individuals with advanced solid cancers, such as breast, prostate, and lung cancer, the occurrence of bone metastasis often affects their quality of life and prognosis. Activation of osteoclasts is a characteristic of osseous

metastasis. Therefore, drugs directed against osteoclast activation have been commonly utilized to treat osseous metastasis; unfortunately, however, they have not been effective in inhibiting the growth of bone marrow cancer cells. On the other hand, other types of resident cells are supposed to contribute to the appearance of cancer cells in areas of osseous metastasis, such as CAFs.

Concerning individuals with prostate carcinoma, the following data of interest have recently been found: that epidermal growth factor receptor EGFR overexpression is a stable and independent marker of EMT of prostate cancers spreading to rigid organs, preferentially bones; that in patients with prostate cancer, a low level of ROR2 correlates with poor endurance and an elevated rate of recurrence; that it appears that caprylic acid facilitates osseous metastasis of prostate carcinoma by a dysregulated adipo-osteogenic equilibrium of bone marrow; that there is loss of tumor-intrinsic interferon signaling and immunogenicity in osseous metastases compared with primary tumors. This could explain why contemporary immunotherapeutics are not successful in prostate cancer osseous metastases and could procure a new therapeutic approach to subdue the ineffectiveness of immune-based treatments in solid cancers. Treatments with PIP5K1α inhibitors could inhibit not solely tumor penetration and metastasis but also improve the host immune system. GPRC5A could be a therapeutic objective and a prognostic marker molecule in advancing prostate carcinoma.

We found big data about individuals with osseous metastases from breast cancer: Asperolide A appears to be a newly released curative medication aspirant in individuals with osseous metastasis. Aiming TGFβ and BMP signaling pathways, together with osteoclast activity, seems to be an encouraging therapeutic approach in preventing breast cancer-induced osteolytic osseous destruction and metastatic growth in metastatic bone niches. TRAF6 inhibitors such as 6877002 (soley or mixed with customary chemotherapy) appear promising for treating metastatic breast carcinoma. Elevated levels of BMP4 and SMAD7 are a prognostic factor for ameliorated recurrence-free endurance and overall endurance, showing the relevance of canonical BMP4 signaling in the suppression of metastasis and emphasizing new therapeutic ways against metastatic illness; aiming the BMP4-SMAD7 signaling axis is a newly released therapeutic approach to fight against metastatic breast carcinoma, an illness whose mortality has not decreased over the past decades. There is also encouraging data of the plausible therapeutic use of BT-isMOF nanoparticles in treating breast carcinoma osseous metastases, and inhibition of IL4R and macrophages could have potential therapeutic benefits.

The following advances should be highlighted concerning lung cancer bone metastasis: LIGHT could play a role in osteolytic osseous illness caused by metastatic NSCLC (individuals diagnosed with NSCLC osseous metastasis have more elevated levels of LIGHT expressed in monocytes than in nonmetastatic tumors and healthy controls). A published model has shown precision with an elevated degree of consistency and whose meantime of prediction of the appearance of bone metastases was 9.46 months earlier than that of diagnosis by osseous scintigraphy. Serum OPG, PTHrP, tP1NP, β-CTx, and the diagnostic model logit (p) were all positively correlated with osseous metastasis advancement. This diagnostic model appears to be an uncomplicated , non-invasive, and sensitive instrument for detecting the appearance and monitoring the advancement of osseous metastases in individuals with lung carcinoma.

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