

Biology of Bonemetastasis and Clinical Medicine

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Abstract: *Bone metastasis in clinical practice is a challenge in current medicine, finding the source of the metastasis, normalizing the Integrity and physiology of bone is the main issues, So a scientific Knowledge with Controlling of these abnormal pathways is needed.*

1. INTRODUCTION

From recent decades there has been a substantial increase in our understanding of the underlying biology of bone metastasis, it is a challenging issue in clinical medicine and is a frequent clinical problem for the internists, the problem is not prognosis, and terminal illness^{1,2,3} but the problem is pain, fracture, hypercalcemia, and spinal cord compression, disability in motion and decreased in quality of life and a sign of incurability and closing to death. Breast, prostate are the top cancers and then kidneys, thyroid, lung are remaining causes of the bone metastasis. Major bone metastasis are osteolytic and Osteoblastic metastasis are commonly associated with prostate cancer and to a much lesser degree by breast cancer and in osteosclerotic variant of myeloma, astrocytoma, glioblastoma multiform, thymoma, carcinoid, nasopharyngeal carcinoma, leptomeningeal gliomatosis, Zolinger Ellison syndrome, cervical carcinoma.^{4,5}

But recent progress in biology of cancer opened the door for this landscape of life, which can be a way to discover more cancer mechanisms and to see the new world of the cell biology.

2. BONE PHYSIOLOGY

The bone is a highly vascular tissue and is the subject of constant remodeling through combined and coordinated activities of two special cells, osteoblast a bone forming cells, and a bone destroyer named osteoclast. osteoblast originates from mesenchymal origin and synthesizes collagen which is resistant to tissue destruction, it is composed of type I collagen, osteoclast originates from hematopoietic stem cells which degrade the bone matrix and minerals in the form of calcium phosphate

Bone exerts important functions in body such as locomotion support and protection of soft tissue calcium and phosphorus, and supporting of bone marrow.^{6,7}

3. GENERAL MECHANISMS OF TUMORS AND BONE METASTASIS

The mechanisms responsible for tumor growth in bone are complex and involve tumor stimulation of osteoblast and osteoclast as well as response of the bone microenvironment.

Metastasis of tumor cells starts with detachment of individual cancer cells from the primary tumor site and invasion to vasculature, migration and adherence to distant capillaries within the bone, extravasation and initial survival within new environment.^{8,9} Bone matrix does not only provides support for bone cells but also has a key role in the regulating the activity of bone cells and tumor cells through several adhesion molecules and growth factors such as, integrins and transforming growth factor beta, respectively the bone microenvironment may act as a premetastatic niche through which the primary tumor can prime distant organs to become receptive to metastasizing tumor cells early during tumorigenesis.^{10,11}

Also, VEGFR1 positive bone marrow derived hematopoietic progenitor cells are able to travel to the sites of future metastasis before tumor cell arrival to facilitate tumor cell metastasis.

Angiogenesis is another mechanisms which provides both nutritional support for tumor ,tumor cell migration local invasion through basement membrane adhesion to vessel endothelium in the target organ and extravasation into the tissue.^{12,13} with detachment from the primary tumors a single tumor cells or cluster of tumor cells can circulate throughout the body and later take up residence in a distant site, marrow macrophage may promote metastatic growth by suppressing tumor induced inflammation.²⁴Once tumors are established in other organs the mortality of cancer increases.

It is generally believed that the tumors nich cause relapse and death. Cancer associated fibroblast in the primary tumors can influence tumor cells to develop properties necessary to become successful bone metastasis. Matrix metalloprotease and cathepsinK secreted are involved in this process.

EGFR signalling in osteoblast directly contributes to the osteolysis or bone resorption it is not expressed on osteoclast, with perturbation of RANK/OPG System.¹⁴

Osteolytic bone metastasis,usually	Osteoblastic bone metastasis,usually
Myeloma,breast,lung,	Prostate,nasopharyngeal,t

4. BREAST CANCER WITH BONE METASTASIS

Bone is a preferred site for breast cancer metastasis and leads to pathological bone loss due to increased osteoclast induced bone resorption .the homing of tumor cells to the bone depends on support of bone microenvironment in which tumor cells prime premetastaticniche. bone metastasis leads to skeletal muscle weakness,due to bone muscle cross talk. once in distant from the primary tumor site and resident in the bone marrow breast cancer cells establish a tight interaction with marrow microenvironment the metastatic cells secrete a plethora of ofosteolytic factors.

With dysregulation of the critical pathways involved in mammary gland development during mammary tumor formation and progression, epidermal growth factor ,fibroblast growth factor, transforming growth factor beta and wnt gene family are all involved in tumor progression. transient cells that contribute to the metastatic microenvironment include red cells, T cells ,platelets all of which are derived from hematopoietic stem cells .

Primary tumor cells release cells that invade surrounding normal tissue via the production of protease and causes tumor cells to invade blood vessels and enter circulation, with hematopoietic cells the tumor cells home to specific organs such as bone the high blood flow in the red marrow and adhesion molecules in tumor cells they bind to stromal cells in the bone marrow ^{15,16}.

Each step in metastatic cascade and specific phenotype can be a target in future for treatment of metastasis. Osteolysis is caused by osteolytic activity of osteoclast not direct tumor infiltration.

In breast cancer, osteoblastic metastasis increases serum alkaline phosphatase level and uptake of technesium diphophonate. The chance of long term survival for patients with bone metastasis in breast canceris usually dismal and only 20% of breast cancer patients live more than five years after the diagnosis of breast cancer.^{17,18}

Multiple extrinsic and intrinsic factors contribute to the homing of tumor cells to bone, expression of 3-4 genes in breast cancer genes is required for cancer cells to home in bone. these genes seem to dictate organ specific metastatic tropism due their ability to compensate for and overcome incompatibilities between the intrinsic growth programs of the disseminated carcinoma cells and the demands imposed by the particular foreign tissue microenvironment around them.

Interleukin11, connective tissue growth factor which encode angiogenic factors or CTGF ,CXCR4, displayed the highest bone metastatic potential, Platelet are source of growth factors adhesion ofbreast cancer cells to platelet causes release of lysophosphatidic acid from platelet and causes angiogenic and osteoclastogenic factor from tumor cells.^{19,20}

Breast lactationis a model for calcium and bone and cytokines mimicking bone status in metastasis. there is increase in calcium concentration in milk secretion, and PTHrP secreted by mammary tissue with effect on bone causes osteolysis, decreased calcium excretion by kidneys and then release of calcium to the circulation which reaches to the milk, CaR expression in mammary tissue has a major role in calcium and PTHrP interaction.

CaR is a calcium receptor, a G protein coupled seven transmembrane domain receptor which responds to small variation in extracellular calcium concentration, the CaR is expressed by breast cancer cells and regulates tumor secretion of PTHrp.

One variant of basal type breast cancer are associated with large size, high tumor grade tumor, poor survival and increased frequency of distant metastasis ,they are triple negative.

EGFR and EGFR ligands may play in breast cancer basal type these types of breast cancer express markers frequently found in basement membrane such markers include keratin 5,17,

p-cadherin and troponin .CTS also will have interesting role in management of breast cancer in future.^{22,23}

5. PROSTATE CANCER METASTASIS TO BONE

The pathophysiology of prostate cancer bone metastasis is complex and involves several different cell types, tumor cells, osteoblast, osteoclast, endothelial cells and an assortment of regulatory proteins e.g. steroid hormone, cytokines and growth factors. activation of osteoclast by tumor cells is initiated by adhesive interaction of tumor cells and bone marrow derived cells which triggers the production of PTHrP by tumor cells, PTHrP stimulates the expression of RANK ligand in osteoblast which promotes the differentiation of osteoclast. tumor cells can directly stimulates osteoclast by osteoclast activating factors such as Interleukin1beta ,interleukin6,interleukin 11 macrophage inflammatory protein 1 alfa, TNFalfa, RANK ligand. Serumendothelin 1 levels are increased in patients with osteoblastic metastasis, collagen and tartarate acid resistant acid phosphatase and urinary level of type I collagen cross linked N-telopeptide are increased.²⁵

Endothelin1, CTGF are main facors for osteoblastic bone metastasis²⁶

The PTHrPis a mediator of 70% of breast and prostate cancer bone metastasis. it is major contributor of prostate cancer bone metastasis.

6. MYELOMAMYELOMA BONE DISEASE

A neoplasms of plasma cells associated with suppression of osteoblastogenesis and increasing activity of osteoclast and lytic bone changes. NFkB, TP53, RB1 all can cause the biologic change of myeloma. In multiple myeloma a complex interaction with bone marrow microenvironment

Intratumor and intertumorheterogeneity contributes to rapid emergence of drug resistance in high risk disease.

Model for molecular pathogenesis of MGUS to MM, the pathogenesis which common is IgH translocation ,hyperdiploidy,del13,that lead directly or indirectly to dysregulation of a CCND gene and also this transition with MYC expression and KRAS mutation ,multiple osteoblastic inhibitors are produced by myeloma cells and bone microenvironment ,WNT inhibitors, DKK1 is an example. downregulation of osteocalcin seen which is a bone marker of osteoblastic activity, Runx2 which is an osteoblastic maturation factor is inhibited by myeloma cells .

Bortizomib a proteasome inhibitor with antimyeloma activity also has bone anabolic drug in myeloma bone disease²⁷

Are cells that have shed into the vasculature or lymphaticsfrom a primary tumors and are carried around the body in the circulation.

7. TREATMENT OF BONE METASTASIS

Bone metastasis is controlled in the majority of cases by inhibiting osteoclastic activity by biphosphonate treatment but this can cause major side effects. Osteonecrosis of jaw is a complication of of biphosphonate use and dental evaluation is needed, Measuring creatinine before bisphosphonate use is mandatory. Mechanisms by which bisphosphonate interfere osteoclast activation is to induce apoptosis by inhibiting farnesyldiphosphate synthase a key enzyme in mevalonate pathway reducing the prenylation of small GTP binding proteins which are essential for the cell survival.

Orthopedic stabilization of osseous metastatic lesions can provide rapid and effective pain relief in patients presenting with significant bone destruction and pathologic fracture.

Despite progress in treatment research in bone metastasis, bisphosphonate and denosomab can not affect response rate or overall survival.

The bone marrow microenvironment in which myeloma cells survive is crucial for tumor initiation and is the mechanisms for radiotherapy and chemotherapy resistance.Radium223 is

a calcium mimetic alfa-emitter that selectively binds to area of increased bone turnover such bone metastasis is a good therapeutic choice in metastatic bone disease. Hypercalcemia of malignancies is usually is a manifestation of advanced malignancy such as bone metastasis. Upto30% of patients with cancer may develop hypercalcemiaduring the course of their disease. Bone metastasis is a major cause of the mechanisms. PTHrp, vitamin D, prostaglandins, cytokines such as TGFalfa, TNFalfaall can causeosteoclastic activity and mediates hypercalcemia of malignancies.

Osteoclasticresorption of bone releases high concentration of ionized calcium and phosphate from the dissolution of bone minerals.

Gastrointestinal manifestations of anorexia, nausea, vomiting are common in association with hypercalcemia and could lead to dehydration, renal involvement manifested by polyuria,

azotemia, weakness psychosis stupor, coma if it is untreated the fatality is high, bisphosphonate or denosomab has a main role for the treatment.²⁸

8. FUTURE OF BONE METASTASIS

Inhibition of SDF activity is another mechanism which is important in future for the controlling bone metastasis. Some future work be soluble RANK and OPG in the treatment

Inhibition SDF, affects the migration of tumor cells in the bone metastasis. Integrin inhibitors are currently and vitamin D analogue have shown promise in in preclinical model of breast cancer metastasis to bone, the mechanism may be inhibition of tumor growth or PTHrp production. Increasing bone formation by myeloma by myelomatous bone is feasible with anti DKK activity which can reverse myeloma bone disease, other new approach to treat bone metastasis is using HSC mobilizing drugs G-CSF and AMD3100 to mobilize the nichengaged dormant DTC to re-enter the cycle.

AMD3100 enhances the susceptibility to chemotherapy to acute myeloid leukemia and myeloma.

Abbreviation:

PTH =parathyroid hormone

CTGF=connective tissue growth factor

PTHrp=parathyroid related protein

RANK=receptor activated nuclear kappa

RANKL=RANK ligand

VCAM-1=vascular cell adhesion molecule

SDF-1=stromal derived factor

NFkB=nucleated factor kappa B

CXCR4=chemokine receptor 4

CaR=calcium receptor

WNT=winglessintegrated retrovirus

DKK1=dickkopf1

OPG=osteoprotegerin

MM=multiple myeloma

MGUS=monoclonal gammopathy of uncertain significance

IgH=Immunoglobulin heavy chain

HSC=hematopoietic stem cells

EGFR=epidermal growth factor receptor

EGF=epidermal growth factor

DTC=disseminated tumor cells

CTS=circulating tumor cells

RB1=retinoblastoma tumor suppression gene

9. CONCLUSION

Bone metastasis management needs a strategy to control the morbidity of cancer patients.

Learning and research on bone metastasis is a way to control cancer systems in future and is the exciting field of the biology of life. This knowledge is important in future for the medical scientist.

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