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Title **Bone and Prostate Cancer Cell Interactions in Metastatic Disease.**

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Summary

The interplay in prostate cancer bone metastases between the “seed” – the prostate cancer cells, and the “soil” – the bone microenvironment, has been increasingly recognised as integral to the remarkable tropism for bone exhibited by prostate cancer. An explosion of research into this area is elucidating the mechanisms involved in this complex crosstalk. Recent developments, including the use of bisphosphonates in metastatic disease, highlight the important role that bone cells play in the development and progression of metastatic prostate cancer. We have reviewed the current literature emphasizing these possible mechanisms indicating possible factors for future treatment directions.

Keywords

bone, prostate, cancer, metastasis, cross-talk

Introduction

A feature of prostate cancer is its predilection to metastasize to bone resulting in pathologic fractures, bone pain and spinal cord compression. These complications severely impact on the patients' quality of life (1).

The majority of prostate cancer bone lesions are osteoblastic (increased deposition of bone) unlike other skeletal metastases which are typically osteolytic due to bone destruction. The complex interplay between prostate cancer and the bone microenvironment will be discussed in detail in the following mini-review.

Molecular Control of Bone Structure and Function

Bone is a biphasic composite material composed of mineral (calcium hydroxyapatite) and organic matrix (osteoid), endowing high strength and resilience to the skeleton. There are two commonly described types of bone tissue: woven bone and lamellar bone. Woven bone is structurally characterised by random orientation of its collagen fibrils and often

high mineral density. It is normally seen in the fetal skeleton at the growth plates. Woven bone in an adult is always indicative of a pathologic state (2, 3).

Lamellar bone which usually replaces woven bone is deposited much more slowly and in a more orderly, layered manner and is therefore much stronger. It requires a preformed solid scaffold and the newly formed lamellae run strictly parallel to the underlying surface (2, 3). The cells involved in bone function include osteoprogenitor cells, osteoblasts, osteoclasts and osteocytes [refer figure 1] (2, 3).

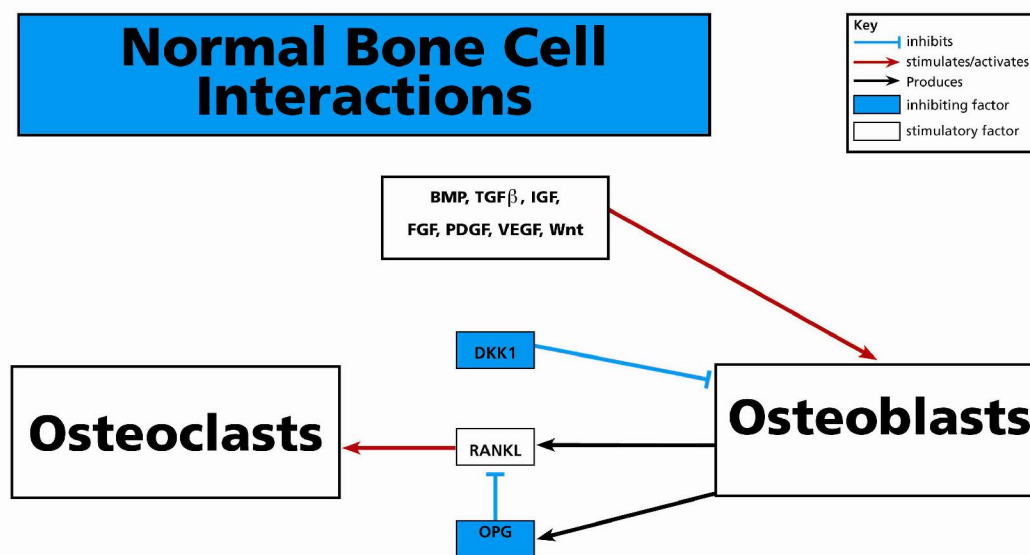


Figure 1 - Bone formation and resorption are linked in normal bone. Osteoblasts form matrix which becomes mineralised to produce bone and osteoclasts break it down. Various osteogenic factors stimulate osteoblast activity, differentiation and proliferation. These include factors such as bone morphogenetic protein (BMP), transforming growth factor- β (TGF- β), insulin-like growth factor (IGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and Wnt. The Wnt antagonist DKK-1 prevents osteoblastic proliferation. Many of these factors are produced by the cells of the bone marrow stroma and extracellular matrix. Osteoblasts control osteoclastic activity through production of cytokines such as receptor activator of nuclear factor- κ B ligand (RANKL) which activates osteoclast differentiation, and Osteoprotegerin (OPG) which acts as a decoy receptor for RANKL.

Osteoblasts line the surface of bone and synthesize, transport and arrange the proteins of the organic matrix. Osteoblasts express various receptors for many hormones (parathyroid hormone [PTH], vitamin D, oestrogen and androgens), cytokines and growth factors (bone morphogenetic proteins [BMPs], transforming growth factor- β [TGF- β], insulin-like growth factor [IGF], endothelin-1 [ET-1], fibroblast growth factor [FGF], and Wnt) all of which control osteoblastic functions (2, 4-6).

The transcription factor RUNX-2 or core-binding factor α 1 (CBFA1) drives the expression of most genes associated with osteoblast differentiation (2-4, 7). It is activated by many growth factors such as FGF, platelet-derived growth factor (PDGF), IGF and TGF- β . RUNX-2 also up-regulates expression of other transcription factors such as Osterix, another essential factor in the control of osteogenesis (7).

Osteoclasts mediate bone resorption, arising from haematopoietic precursor cells of the monocyte-macrophage lineage (1-4). Osteoclast differentiation, maturation and activation is dependent on cytokines and growth factors including Interleukin (IL)-1, IL-3, IL-6, IL-11, tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), parathyroid hormone (PTH), activated vitamin D, and thyroxine (T_4) (1, 2, 4).

Both bone stromal cells and osteoblasts produce important factors mediating bone metabolism such as RANK (Receptor Activator for Nuclear factor κ B), RANK ligand (RANKL), and osteoprotegerin (OPG). RANK is a member of the TNF family of receptors mainly expressed on the cell surface of osteoclast precursors. RANKL is expressed on the surface of osteoblasts and bone marrow stromal cells and is released by activated T cells (1, 2, 4). RANKL's major role is stimulation of osteoclast formation, fusion, differentiation, activation and survival. Most of the systemic osteotropic factors such as PTH, activated Vitamin D and prostaglandin E_2 induce osteoclast formation by increasing expression of RANKL on stromal cells and osteoblasts rather than a direct effect on the osteoclast precursors (4).

When RANKL binds the RANK receptor on osteoclast precursors, it induces osteoclast formation. The soluble protein OPG acting as a decoy RANK receptor inhibits osteoclast differentiation and activation (2, 4). Ratio of RANKL to OPG regulates osteoclast activity allowing osteoblasts and stromal cells to regulate osteoclast function influencing bone homeostasis.

Wnt proteins are primarily involved in developmental control of body axis symmetry and branching morphogenesis *in utero* (8, 9). In mature tissues, Wnts are involved in self-renewal of stem cells and maintenance of many normal tissues as well as oncogenesis (10). Disruption of Wnt signalling results in limb defects in the developing embryo. Adult bone remodelling is also affected by defects in Wnt antagonists (9).

Human and mouse studies suggest that Wnt signalling increases bone mass at least in part by stimulating osteoblastogenesis. There appears to be a temporal importance of Wnt signalling in osteoblast differentiation. Disruption of Wnt signalling by expression of the Wnt antagonists Dkk-1 and 2 blocks osteoblast differentiation in immature osteoblasts but is required to promote terminal differentiation in late stage osteoblasts. Mesenchymal stem cells from which osteoblasts derive can differentiate into several cell types and there is considerable evidence that Wnt signalling stimulates osteoblastogenesis and represses alternate differentiation pathways (9). Wnt signalling increases expression of osteoblastogenic transcription factors such as RUNX-2 and Osterix possibly by direct binding of a β -catenin/T Cell Factor (TCF) complex to the RUNX-2 promoter (9). Recent studies have suggested that Wnt signalling increases the growth rate of undifferentiated and proliferating osteoblast precursor populations and inhibit osteoblast apoptosis increasing numbers and survival (9).

Wnt activation may also affect bone formation by increasing the mineralizing activity of osteoblasts. Activation of β -catenin in osteoblasts specifically increases expression of type I collagen (a major component of the organic matrix). It also affects osteoclast function by increasing osteoblastic expression of OPG, decreasing osteoclast differentiation and bone resorption (9).

Bone Remodelling

Skeletal remodelling involves substitution or replacement of packets of bone and occurs continuously throughout life as a means of preserving the mechanical integrity of the skeleton. During growth it contributes to bone maturation. In the adult it provides metabolically active tissue for calcium homeostasis, eliminates avascular, necrotic bone compartments and prevents fatigue by local repair of micro-cracks and fractures (2, 3).

Bone remodelling is characterised by the activation-resorption-formation sequence which has a duration of approximately 3 to 4 months in humans. It is initiated with the activation of resting cell populations on or near a bone surface. Osteoclasts are the first to invade the area and resorb bone, closely followed by osteoblasts that fill the excavated site with new bone matrix. Bone formation and resorption are both temporally and quantitatively coupled in optimal conditions, such that the activity of osteoclasts and osteoblasts is tightly coordinated

The remodelling rate varies from bone to bone and with age. It is activated by various growth hormones, thyroid and parathyroid hormones and inhibited by calcitonin, cortisone and possibly calcium (3).

Effects of Hormones and Aging on Bone

Peak bone mass is achieved early in adulthood and is related to nutrition, level of physical activity, age and hormonal status. Men experience a gradual age-related loss of bone mineral density (BMD) of 7-12% per decade after 30 years of age.

Bone turnover in males is active before 25 years of age, decreases rapidly up to 40 years of age when it slows reaching a nadir at 55-60 years of age. After 60 years of age, bone resorption as measured by bone turnover markers increases, (as does remodelling rate), whilst bone formation remains stable therefore leading to an overall negative balance (3, 11, 12). Osteoporosis in men however is rarely encountered in men before 70 years of age.

Balanced bone remodelling depends on appropriate hormonal signals. As previously mentioned both osteoclasts and osteoblasts have receptors for oestrogens and androgens (5, 6, 13). Androgens have direct actions on osteoblasts inducing proliferation and differentiation, and inhibiting apoptosis (6).

Testosterone was felt to be most important in men for control of bone metabolism but recent evidence suggests that oestrogens play the major role, especially in elderly men controlling bone resorption (5, 6, 14, 15).

Age-related decline in BMD may be due to reduced oestradiol and testosterone bioavailability with age-related increases in sex hormone binding globulin (SHBG). This reduces testosterone available for conversion to oestradiol through aromatization, decreasing the protective effects of oestrogen. Thus bone resorption is increased, reducing BMD (5, 14, 15).

Oestrogen may act in concert with paracrine factors secreted by osteoblasts reducing pro-resorptive cytokines such as IL-1, TNF- α , IL-6 M-CSF and PGE₂ and increasing the anti-resorptive cytokine TGF- β . Oestrogen appears to increase OPG production and downregulates the expression of RANKL altering the resorptive function of osteoclasts via the RANKL/OPG system (13, 16).

Androgen deprivation therapy produces significant osteoporosis reducing BMD by 3-7% per year. This exacerbates pre-existing bone loss, leading to osteopenia or osteoporosis in nearly 90% of patients after 1 year of treatment and a fivefold increase in skeletal fractures for men treated with androgen deprivation compared to age-matched controls (5, 15). Whether or not this active, fertile "soil" increases the risk of bone metastases in prostate cancer is currently unknown.

Androgen deprivation therapy has been increasingly broadened and is now prescribed for locally advanced disease and biochemical relapse after local therapies. Many men are now being treated at an early age for longer periods (15, 17). The potential and actual

major public health cost due to osteoporotic secondary complications in prostate cancer patients is increasingly recognized.

Molecular Biology of Prostate Cancer Metastases; Cross Talk and Interaction with the Bone Microenvironment in Metastatic Disease

Effects of Bone on Prostate Cancer

The bone microenvironment has direct effects on prostate cancer cells, which may explain the tropism of prostate cancer (CaP) for bone. Many of the factors discussed previously produced by bone marrow stromal cells, osteoclasts and osteoblasts also affect the prostate cancer cells [refer figure 2].

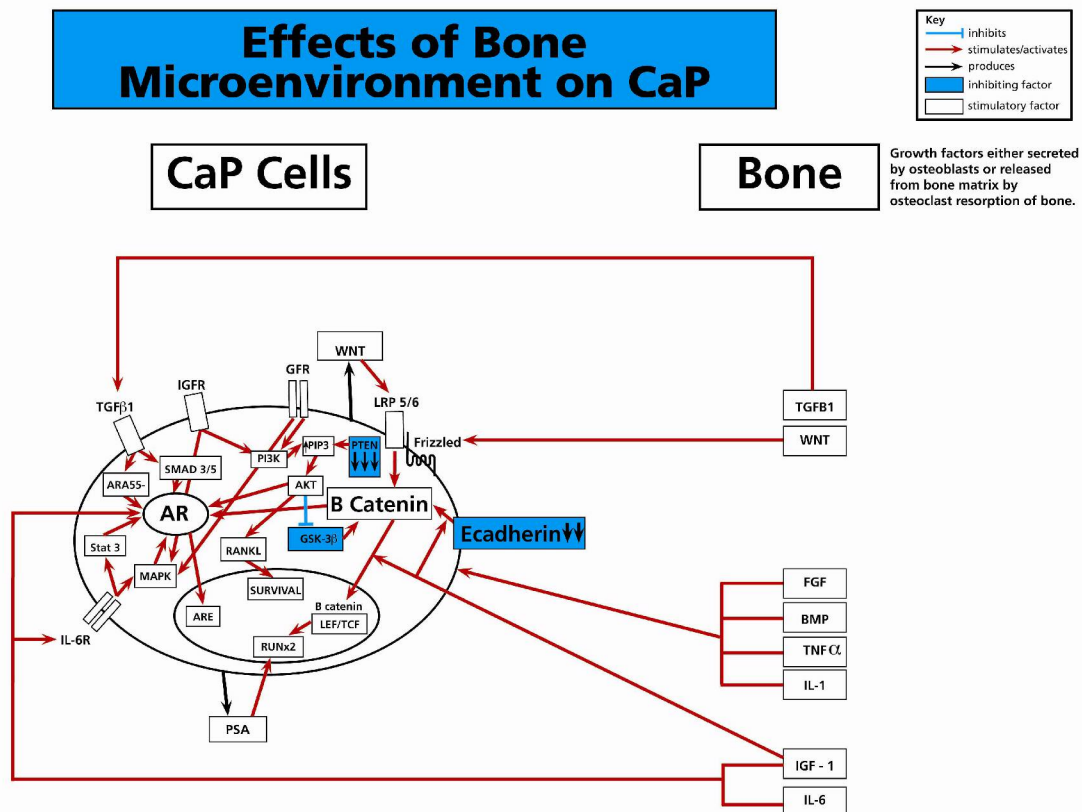


Figure 2 – Summary of interactions between bone microenvironment and prostate cancer cells. Various cytokines and growth factors produced by or released from the bone tissue interact with their receptors on the prostate cancer cell (notated for example as IGFR for

the insulin-like growth factor receptor and the Wnt receptor frizzled and its co-receptor LRP5 and 6 on the diagram). Once stimulated these receptors act via various intracellular signalling pathways such as the SMAD, androgen receptor associated protein 55 (ARA55), transducers and activators of transcription (STAT), phosphatidylinositol 3'-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK) signal transducers. These act on various down stream effectors but many interact with the androgen receptor itself (AR) which once activated translocates to the nucleus and activates the androgen response elements (ARE) to initiate transcription of various androgen sensitive genes. Beta catenin which is increased when the Wnt pathway is activated controls transcription factors of Lymphoid Enhancer-Binding Factor/T Cell Factor (LEF/TCF) family. Beta catenin is targeted for constitutive degradation by glycogen synthase kinase 3 β (GSK-3 β). In the absence of Wnt ligand, GSK phosphorylates the bound β -catenin which directs it for ubiquination and subsequent proteasomal degradation thereby maintaining low levels of cytoplasmic β -catenin. The PI3K/AKT pathway can inhibit the activity of GSK-3 β thereby preventing degradation of β catenin and increased levels. E cadherin is involved in cell-cell adhesion and is down-regulated in metastatic prostate cancer. It also has β catenin complexed to it and therefore when downregulated may increase the pool of available β catenin intracellularly. Phosphatase and tensin homologue (PTEN) causes cell-cycle arrest and apoptosis as well as inhibition of cell motility. PTEN function is often downregulated or lost in prostate cancer which can increase activity of the PI3/AKT pathway.

Factors specific to bone are involved in chemotaxis and attachment of the prostate cancer cell to bone. The bone protein SPARC has been implicated as an important chemotactic factor, as has the cytokine CXCL12 also known as Stromal derived factor (SDF-1). These, and specific integrins (some of which are upregulated by TGF- β) may mediate the initial attraction and attachment of prostate cancer cells to the bone tissue and promote metastatic deposit growth (18-20).

Growth Factors

The bone matrix has several growth factors bound within its structure and once released upon bone resorption may promote growth of the tumour. These include IGF, TGF- β , BMPs and FGF.

IGF-1

The IGFs abundant in bone are potent mitogens stimulating the growth of tumour cells. Once bound IGFs are released via bone resorption, they can enhance metastasis in two ways: by increasing cell numbers (proliferation); and by attracting the tumour cells to bone (chemotaxis) (21). Prostate cancer cells can also increase IGF levels through degradation of the IGFBPs, potentiating these effects. IGF-1 activates the transcriptional targets of the androgen receptor (AR) via the PI-3K/AKT pathway, as well as several anti-apoptotic mechanisms (22).

TGF- β

Bone is a rich source of TGF- β . Studies have indicated that low levels of TGF- β result in cellular proliferation of prostate cancer (21). High levels of TGF- β paradoxically inhibit proliferation.

Effects of Prostate Cancer on Bone

Prostate cancer cells alter bone homeostasis by secreting factors directly affecting osteoblast function, or influencing bone formation indirectly by modifying the bone matrix or microenvironment. Cancer cells synthesize and deposit bone matrix proteins such as osteopontin, osteocalcin, osteonectin and bone sialoprotein within the bone. Through this osteomimetic ability they may directly contribute to bone formation (16, 23).

The prostate cancer cells produce both pro-osteoblastic and pro-osteoclastic factors. Some factors are able to function in both manners, depending on timing of production or concentration. Whilst radiological secondaries appear osteoblastic, histology and bone resorption and formation marker evidence indicates they are mixed osteoblastic and

osteolytic lesions. Osteoblastic metastases form on trabecular bone at sites of prior osteoclastic resorption and are characterised by the weak woven bone tissue predisposing the site to fracture. The increased bone production is via an overall increase in bone remodelling with induction of osteoblastic mediated bone formation outweighing osteoclastic resorption (7, 18, 24). The exact mechanisms by which this occurs are likely to be multiple and are still poorly understood.

Pro-Osteolytic Factors Produced by Prostate Cancer Cells

As noted, it appears osteolysis is required prior to osteoblastic bone deposition in metastatic deposits. The cancer cells produce several pro-osteolytic factors which can enhance this initial bone resorption [refer figure 3].

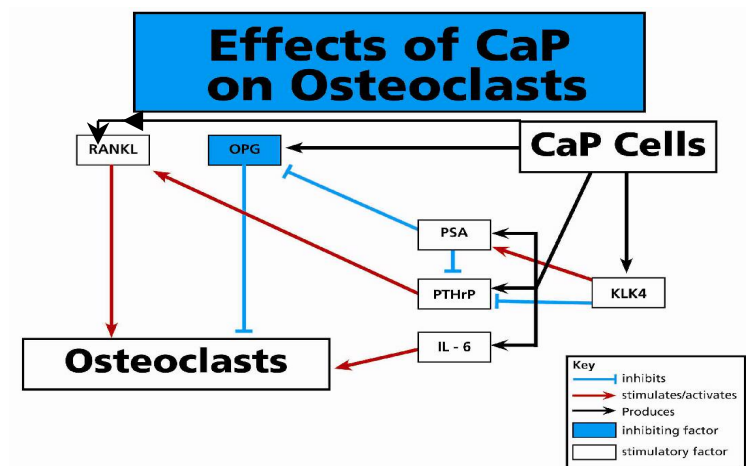


Figure 3 – Summary of interactions between prostate cancer cells and osteoclasts. RANKL stimulates osteoclast differentiation and action, and decreases apoptosis. OPG acts as a decoy receptor for RANK. The balance between OPG and RANKL is critical in controlling osteoclast activity. The prostate cancer cells produce factors which can both stimulate or inhibit the activity and regulation of osteoclasts.

Receptor activator of NFκB ligand (RANKL)

Prostate cancer cells produce RANKL and can directly initiate osteoclastogenesis and therefore stimulate bone resorption (16, 18, 23-25). Upregulation and expression of

RANKL by prostate cancer cells and osteoblasts is controlled by several factors produced by the prostate cancer cells themselves and therefore may act in a paracrine and/or autocrine fashion. These factors include PTHrP, IL-6 and 1 and PSA.

Parathyroid hormone related protein (PTHrP), Interleukin-1 and -6 (IL-1 and IL-6)

PTHrP is an endocrine hormone that evokes the same biological activity at the parathyroid hormone receptor as PTH, increasing bone resorption. PTHrP is produced by prostate cancer cells and leads to expression of RANKL on bone marrow stromal cells, inducing formation of osteoclasts and bone resorption. This releases among other factors, TGF- β , which further increases PTHrP production by prostate cancer cells (4, 24, 26). PTHrP may protect prostate cancer cells and osteoblasts from apoptosis and act as a mitogen to promote tumour growth in addition to its osteoclastogenic properties (18).

Other potent osteoclastogenic factors produced by prostate cancer cells include IL-1 and IL-6 (16, 18, 26). IL-6 is a potent stimulator of osteoclast formation and can enhance the effects of PTHrP on the formation of osteoclasts. Elevated serum levels of IL-6 correlate strongly with objective markers of prostate cancer morbidity and suggest that it may be useful as a marker of prostate cancer activity and possibly also disease progression (4, 16, 18, 26)

Matrix Metalloproteinases (MMPs)

MMPs promote osteolysis and possibly metastasis by degrading bone matrix and are secreted by prostate cancer cells [refer figure 4]. MMP-2 and MMP-9 blood and urine levels are increased in patients with prostate metastases. MMPs are also active during osteoclast recruitment to sites of bone remodelling (16). The mechanism by which prostate cancer produced MMPs induce bone resorption is not clear. It may involve induction of osteoclastogenesis, as inhibition of MMPs reduces the number of osteoclasts associated with prostate tumour growth in human bone implants in an experimental mouse model (18, 27).

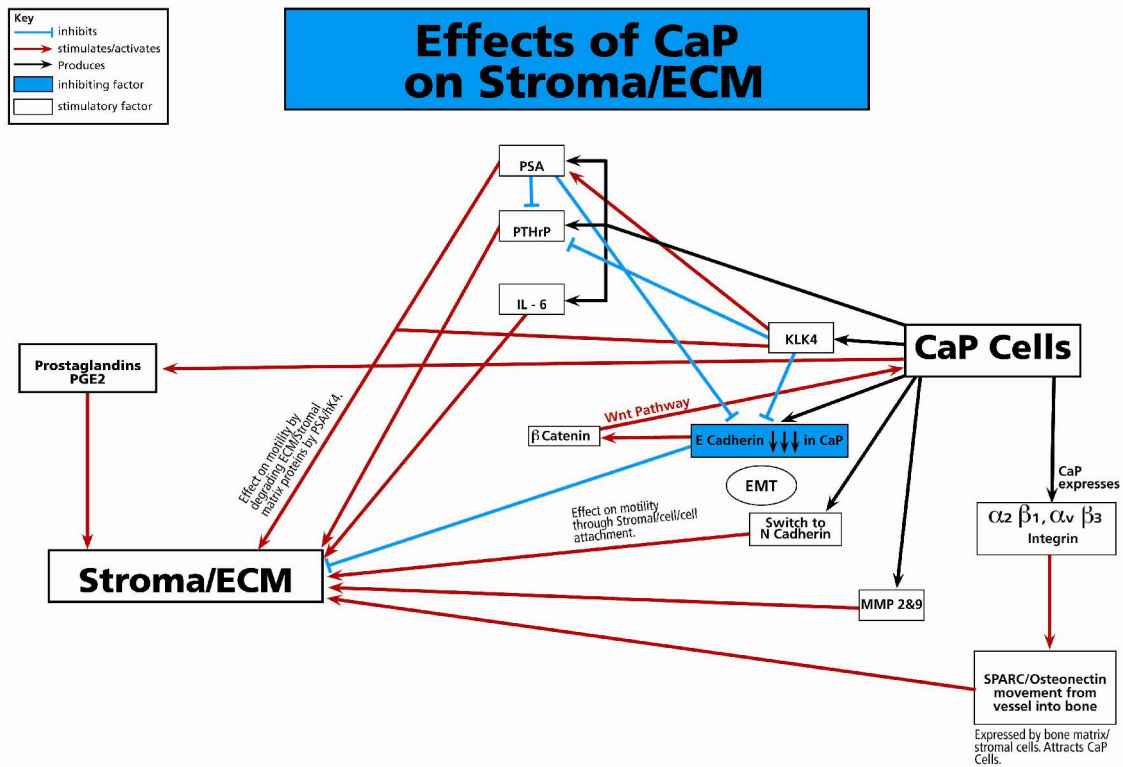


Figure 4 – Summary of interactions between prostate cancer cells and bone marrow stroma and extracellular matrix. Much of the effects of prostate cancer cells on the ECM pertain to metastasis and epithelial to mesenchymal transformation (EMT). EMT is necessary for the successful spread of cancer cells from the prostate to the bone metastatic site.

Kallikrein Related Proteases

The kallikrein related proteases, a family of serine proteases, have specific involvement in both normal prostate and prostate cancer. Prostate specific antigen (PSA) or KLK3 is one such kallikrein related protease. PSA hydrolyses the seminal vesicle proteins, seminogelin I and II in ejaculate, liquefying the seminal clot (28). PSA has recently been shown to decrease OPG mRNA expression and increase RANKL mRNA expression suggesting that PSA may induce osteoclast formation (29)

Pro-Osteoblastic Factors Produced by Prostate Cancer Cells

Multiple products of prostate cancer promote the hallmarks of the osteoblastic reaction – increased osteoid surface, osteoid volume and mineralization rate [refer figure 5].

Osteoprotegerin (OPG)

Studies suggest a positive association between the presence of metastatic prostate cancer and raised OPG levels. Whilst most OPG is likely to be produced by bone marrow cells, prostate cancer cells themselves have also been shown to produce OPG (26).

OPG in human prostate cancer cells has also been shown to be a survival factor due to its ability to bind TRAIL (a TNF related apoptosis inducing ligand) suppressing apoptosis. Production of OPG may therefore be a strategy for survival by providing a decoy target for TRAIL produced in and around tumour foci by patient monocytes and other cell types (24, 26, 30).

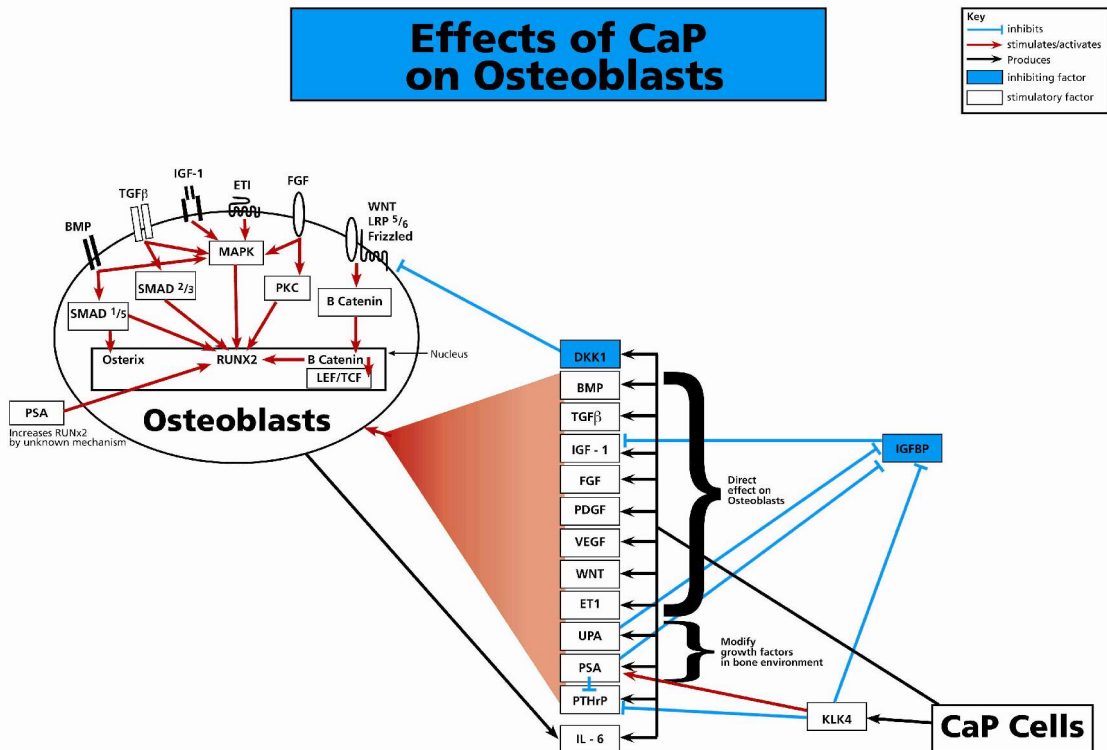


Figure 5 – Details of interaction between prostate cancer cells and osteoblasts. RUNX2 controls transcription factors and when activated increases Osteocalcin, Bone

Sialoprotein, Osteopontin, Alkaline Phosphatase and Type I collagen. Protein kinase C (PKC) is another intracellular messenger transduction system. Osterix is another controller of transcription factors similar to RUNX2.

Bone Morphogenetic Proteins (BMPs) and Transforming Growth Factor- β (TGF- β)

BMPs and TGF- β are members of the TGF- β superfamily. BMPs have multiple functions in bone including apoptosis, differentiation, proliferation and morphogenesis. Target genes of the BMPs in osteoblasts include OPG and RUNX-2 (18, 24).

BMPs' can induce uncommitted stem cells and myoblasts to express osteoblast characteristics such as alkaline phosphatase or osteocalcin. Their osteogenic properties appear to be specific to the differentiation stage of target cells. They do not stimulate mature osteoblasts or fibroblasts to increase expression of these proteins (18, 24). Prostate carcinoma cells produce increasing levels of BMPs as they progress to a more aggressive phenotype suggesting upregulation of BMP expression by cancer cells in bone is a critical component in the development of osteoblastic lesions (7, 18, 24).

TGF- β upregulates RUNX-2 and similar controllers of osteogenesis. Increased TGF- β levels are seen in patients with prostate cancer bone metastases compared to those without (7, 26). TGF- β 1 may act directly on the stroma regulating angiogenesis and tumour progression as well as induction of differentiation in bone cell populations, induction of growth/survival factors by/for tumour cells and regulation of tumour cell attachment to matrices (16, 26).

Insulin-like Growth Factor -1 (IGF-1)

Serum levels of IGF-1 correlate with risk of prostate cancer and the IGF-1 receptor is required for neoplastic transformation (31). Serum levels of IGF-binding proteins (IGFBPS) are inversely related to the risk of developing prostate cancer. IGF-1 binds receptors on osteoblasts activating RUNX-2 (7, 18). This may provide a link between IGF-1 and the development of osteoblastic metastases.

Endothelin-1 (ET-1)

Endothelin-1 is a potent vasoconstrictor that belongs to a family of three 21-amino-acid peptides. ET-1's effects are mediated mainly through the ET_A receptor. ET-1 has been detected in osteocytes, osteoblasts, osteoclasts and vascular endothelial cells. ET-1 stimulates mitogenesis in osteoblasts which have both ET_A and ET_B receptors. It also enhances the effects of other osteoblast-stimulatory factors such as BMP-7 to induce bone formation (4, 18, 24, 32).

Prostate epithelium produces ET-1 and has high affinity receptors throughout the gland. ET-1 levels are increased in patients with osteoblastic metastases from prostate cancer (4). Tumour produced ET-1 may have paracrine (on bone cells) and/or autocrine effects (on tumour growth and apoptosis). Exogenous ET-1 increases prostate cancer cell proliferation and augments the effects of IGF-1, PDGF, EGF and FGF-2. It has also been shown that ET-1 production is increased by prostate cancer cells in contact with bone (7, 18, 24, 32). Substantial data associates ET-1 with osteoblastic metastases in prostate cancer.

Vascular Endothelial Growth Factor (VEGF)

VEGF is a key regulator of physiologic and pathophysiologic angiogenesis. VEGF promotes endothelial cell proliferation, survival and migration. The effects of VEGF are mediated via several receptors. The two key receptor tyrosine kinases are VEGFR-1 and VEGFR-2. VEGF has previously been shown to regulate bone formation indirectly by controlling vascularity within the developing growth plate (7). VEGF has a direct effect on bone formation by stimulating migration and proliferation of human osteoblasts (33).

Prostate cancer cells produce VEGF facilitating tumour growth by enhancing angiogenesis and possibly migratory ability. The VEGF produced by tumour cells binds neuropilin-1 on pre-osteoblasts inducing osteoblast differentiation and in conjunction with other tumour related pro-osteoblastic factors, results in osteosclerotic lesions (7, 33).

Kallikrein Related Proteases and Urinary Plasminogen Activator (uPA)

PSA and KLK2 mediate cell proliferation in both the normal and malignant prostate by interactions with the insulin-like growth factor axis. PSA has potent mitogenic activity for osteoblasts. This may be through elevation of IGF-1 acting as an osteoblastic growth factor increasing bone deposition. PSA may achieve this by degrading IGFBP3 thereby increasing bioavailability of IGF-1. Another pathway may be through PSA activating the latent form of TGF- β (4, 26, 28, 29, 34). PSA may also have a direct role in modulation of genes involved in bone remodelling, including upregulation of genes such as RUNX-2, osteopontin, and TGF- β (29).

PSA increases bone deposition by cleaving PTHrP (18). PTHrP has multiple effects on the bone and prostate cancer cell populations but its degradation may reduce bone resorption thereby tending toward increased deposition (4, 7, 28, 29, 34, 35).

uPA is another serine protease produced by prostate cancer which acts as an osteoblast growth factor. This may be due to increasing IGF-1 levels by hydrolysing IGFBP-3 and activating latent growth factors such as TGF- β similarly to PSA (4, 7, 18).

Wnts

The Wnt pathway has been implicated in the development of osteoblastic metastases in prostate cancer in several ways. Wnt signalling by the prostate cancer cells may promote osteomimicry. Expression by tumour cells of the bone matrix protein osteopontin (OPN), the OPN receptor CD44 and RUNX2, and the ability to produce mineralised matrix has been noted. The Wnt pathway may be involved in this osteomimicry in that both OPN and CD44 are Wnt regulated genes and the canonical Wnts stimulate osteoblast mineralization and differentiation (8, 9).

Other evidence pointing to the involvement of the Wnt pathway is conflicting, indicating the complexity of the Wnt pathway and its role in bone metastases. Hall *et al* have suggested an elegant mechanism of Wnt involvement in prostate cancer osteoblastic metastases (9). They have suggested that the involvement of Wnt agonists and

antagonists are integrated with many of the previously mentioned factors to produce a phasic model. Refer to figure 6 for an overview of interactions between prostate cancer cells and bone.

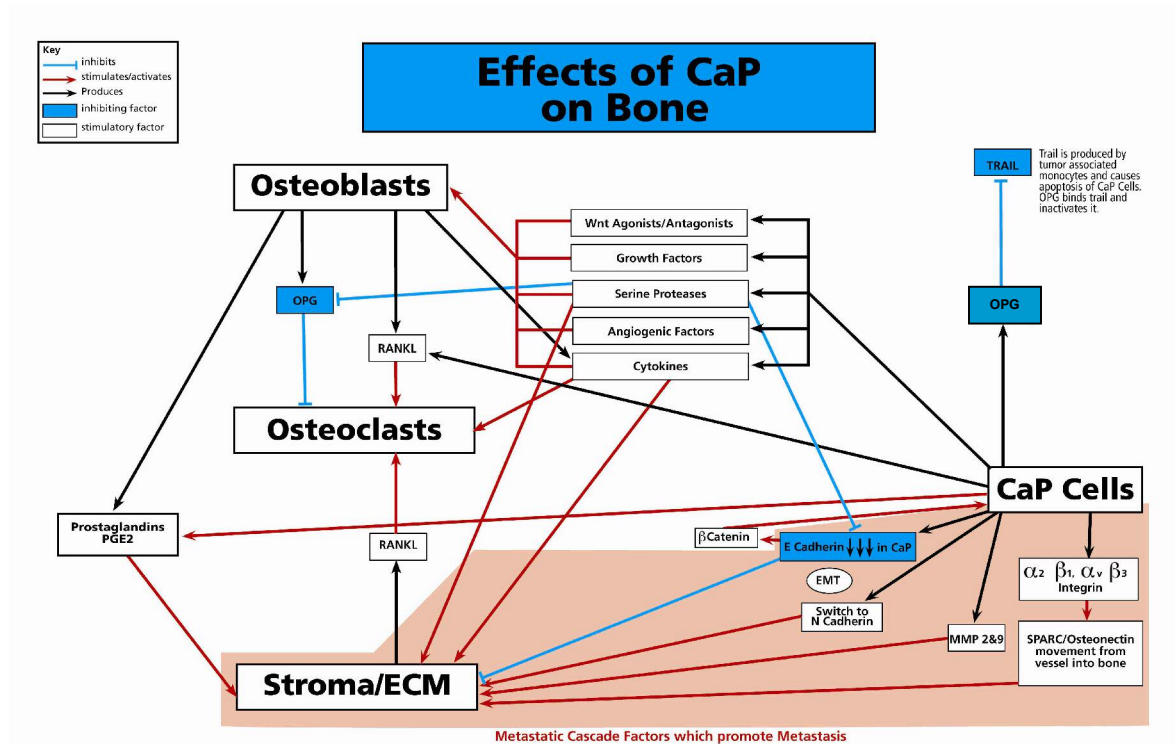


Figure 6 – Overview of the complex interactions between prostate cancer cells and the bone microenvironment promoting tumour establishment and growth of osteoblastic metastases. Shaded area illustrates metastatic cascade factors which promote prostate cancer cell metastases from primary cancer deposit.

Integrated Phasic Model of Metastatic Prostate Cancer

In this model, initially the prostate cancer cells target bone and establish metastases and produce pro-osteolytic factors such as RANKL, IL-6, PTHrP and the Wnt antagonist and inhibitor of osteoblastic activity dickkopf-1 (DKK-1). The osteolytic activity releases growth factors stored in the bone, modifying the bone microenvironment which then alters the prostate cancer phenotype. Tumour cells then produce osteoblastic factors including BMP, PTHrP (which can act as an anabolic factor through inhibition of

osteoblastic apoptosis) and factors which block osteoclastic activity such as OPG. DKK-1 expression also decreases activating the Wnt pathway which increases osteogenesis. This therefore transforms an initial osteolytic phenotype to an osteoblastic one. As the deposit expands, it outgrows its initial blood supply producing hypoxia, inducing VEGF and ET-1 expression to promote angiogenesis. Both the cytokines also have osteoblastic activity, enhancing bone production (9).

This model may explain why apparently conflicting data has been noted by various research groups due to the phasic activity of the factors involved.

Conclusion

As is obvious from the preceding discussion and figures, the complex interplay of the pathways involved is significant. As new technologies such as micro-array evolve and are used more extensively, this complexity is likely to continue to grow. A continued challenge for researchers is identification and characterisation of the important pathways and components of the bone/cancer interplay. Only through this dedication will one day effective therapeutic interventions become available to impact on this pre-eminent issue in men's health.

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