

Reciprocal cross-talk between Prostaglandin E2 and bone in prostate cancer: a current review

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KEY WORDS

prostate cancer ▶ PGE2 ▶ bone metabolism ▶ bone metastases

ABSTRACT

In this review we analyzed the role of PGE2 as a possible regulator of bone metabolism and bone metastases in prostate cancer. Published studies were identified by searching computerized bibliographic systems from January 1st, 2000 to July 1st, 2011.

PGE2 represents a key factor in the modulation of bone metabolism and bone metastatic disease in prostate cancer interacting with bone regulatory signals including the RANK/RANKL/OPG system and Wnt pathways. A high concentration of PGE2 exerts a prevalent stimulatory effect on osteoclastogenesis via OPG/RANK/RANKL axis activation and a inhibitory effect on osteoblastogenesis through inhibition of Wnt pathway. An inversely low level of PGE2 exerts a stimulatory effect on osteoblastogenesis via activation of the Wnt pathway.

Our finding suggests that PGE2 acts as a regulator in maintaining normal bone mass and indicate a mechanism whereby chemical manipulation of PGE2 levels or signaling may be therapeutically beneficial for prostate cancer treatment.

INTRODUCTION

Prostate cancer (PCa) is the most commonly non-skin diagnosed neoplasm among men in the industrialized world and is a leading cause of cancer death in men in the United States [1, 2]. The most common site of PCa metastasis is the bone. About 90% of patients who have died of advanced hormone refractory prostate cancer had clinical evidence of bone metastases and 100% has histologic bone involvement [3, 4].

Prostaglandins (PG) have been implicated in the development and progression of many cancers, including colonic, mammary, and prostate cancers, and COX (Prostaglandin Endoperoxide H Synthase), the enzyme that modulates PG synthesis, is an important molecular target in cancer therapy [5, 6]. COX metabolizes Arachidonic acid to Prostaglandin (PG) H2. PGH2 is also converted to PGE2, PGD2, PGF2 α , PGI2 and Thromboxane (Tx) A2 [7].

In prostate tissue PGE2 is the most abundant derivative of PGH2 and its overexpression has been reported in prostate cancer [8]. PGE2 acts by multiple mechanisms such as stimulating cell growth and inflammation, promoting proliferation and survival of cancer cells, upregulating antiapoptotic proteins and regulating immune system [9, 10, 11]. Prostaglandin E2, binding to G-protein-coupled membrane receptors (EP1-EP4), expressed by prostate cancer cell, stimulate the proliferation

of prostatic neoplasm and modulate kinase pathways, including those regulated by SRC, PI3K/AKT, and PKA [12-17]. The PGE2 concentration is almost 10-fold higher in prostate cancer respect to normal prostatic tissue and elevated levels of this prostaglandin are associated with angiogenesis, cell proliferation and migration [18]. The levels of PGE2 are about 2.5-fold higher in high invasive prostate cancer cell than low invasive prostate cancer cells [19]. Nevertheless the depletion or inhibition of PGE2 increases apoptosis of cancer cells. Takahashi and al. hypothesized that this event is related with a direct action of bone microenvironment rather than a direct control on cancer cell [9].

In this review we analyzed the role of PGE2 as a possible regulator of bone metabolism and bone metastases in prostate cancer.

MATERIALS AND METHODS

Search methods for identification of studies

We conducted a systematic search of relevant full-length papers identified by searching computerized bibliographic systems (INDEX MEDICUS/MEDLINE, SCOPUS, LIFE SCIENCE JOURNALS) from 1 January 2000 to the present (the last systematic search was dated 1 July 2011).

Studies were identified using the following as search query: Prostate Cancer, Bone metabolism, Bone metastasis, Prostaglandin E2, RANK, RANKL, OPG, and Wnt pathway.

Additional papers were found by hand-searching the reference lists of relevant papers screened for pertinent information. Three independent reviewers performed all aspects of the search strategy and reviewed the full text articles in detail to identify articles that addressed the relationship between PGE2 and bone in prostate cancer.

Selection of studies

Working independently, reviewers screened all eligible studies in full text. Discrepancies were resolved by a fourth reviewer or by consensus.

To be included in this review, articles had to (1) evaluate the relationship of PGE2 and bone metabolism and/or bone metastases in prostate cancer, (2) from a full-text peer reviewed journal, and (3) contain an original data analysis. Articles were excluded if the study (1) presented only as meeting abstracts or case report, (2) was not in English, (3) did not analyze a reciprocal relationship of PGE2 and bone, or (4) had inappropriate design.

Data Extraction and Quality Assessment

For each study the following data were abstracted: population source, sample size, adequacy of study, statistical methods, outcome assessed. Where relevant results for a study are reported in more than one paper, those based on the greatest number of cases are used.

Hard copies of all included articles were obtained and read in full. Based on the availability of relevant data the search yielded 48 relevant articles.

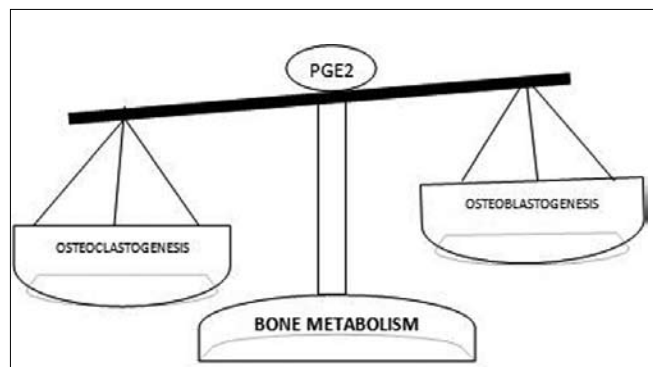


Fig. 1. A schematic representation of bone metabolism regulation orchestrated by PGE2 concentration. High levels of PGE2 stimulate osteoclast differentiation through inhibition of OPG secretion, induction of RANKL expression in osteoblasts and stimulation of RANK expression in osteoclasts. Low levels of PGE2 results in defective osteoblast secretion of RANKL and impaired osteoclast formation, stimulation of preosteoblast cell growth, differentiation and Wnt signaling.

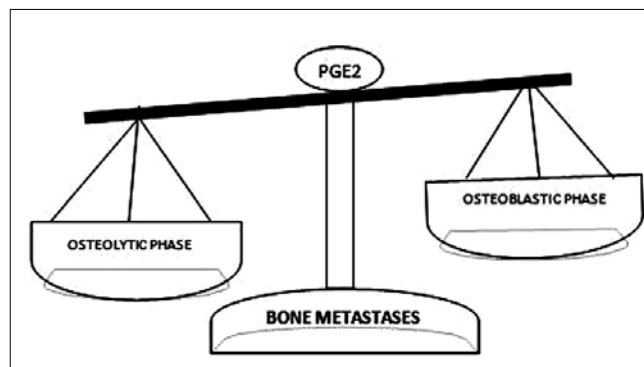


Fig. 2. A schematic representation of aberrant expression of PGE2 in prostate cancer resulting in metabolic bone diseases. High-dose of PGE2 increased expression of Dkk-1 and sFRP, two potent Wnt inhibitors, predominant in osteolytic phase of Pca bone metastases. In more advanced osteoblastic phase of prostate cancer bone metastases, low dose of PGE2 can promote osteoblastogenesis activating Wnt pathway.

RESULTS

Bone tissue remodeling results from the balanced cooperation of osteoblasts and osteoclasts: Osteoclasts are principally responsible of bone resorption, while osteoblasts are bone-forming cells that cause bone mineralization [20]. The relationship between these cells is mediated by receptor activator of nuclear factor B ligand (RANKL) on the osteoblasts and receptor activator of nuclear factor B (RANK) on the osteoclast surface. Stimulation of RANK by its ligand induces osteoclast formation and activation. Osteoblast precursor cells also produce osteoprotegerin (OPG), a decoy receptor that binds to RANKL and thus inhibits RANKL–RANK interaction and osteoclast activation [21]. The RANKL/OPG ratio has a key role in the regulation of the osteoclasts formation and differentiation [22].

PGE2 represent a key factor that modulates bone metabolism, stimulating bone formation and bone resorption, but in favor of bone formation and, thus, increasing bone mass and bone strength [23, 24, 25]. The PGE2 system interacts with bone regulatory signals including the RANK/RANKL/OPG and Wnt pathways.

Effects of PGE2 on RANK/RANKL/OPG signaling pathway

RANK is a member of the tumor necrosis factor receptor (TNFR) family expressed by mature osteoclasts and its precursors, dendritic cells, as well as breast and prostate cancer cells [26, 27]. RANKL is a tumor necrosis factor (TNF)-related cytokine expressed principally by osteoblasts and their immature precursors, megakaryocytes, and lymphocytes [28, 29]. OPG is a soluble glycoprotein secreted by osteoblasts and bone marrow stromal cells, which prevents RANKL/RANK interaction and hence osteoclastogenesis [30].

PGE2 plays a critical role in bone remodeling and bone metastatic disease, stimulating osteoclast differentiation through inhibition of OPG secretion, induction of RANKL expression in osteoblasts, and stimulation of RANK expression in osteoclasts [20, 31–34]. PGE2 directly accelerate the physiological process of osteoclastogenesis and the development of large mature osteoclasts and indirectly regulate osteoclast numbers and morphology. Both stimulatory and inhibitory effects have been documented and the response may depend on the stage of development of the osteoclasts and on the prostaglandin receptors expressed [35] (Fig. 1). PGE2 initially exerts an inhibitory effect on RANKL activity and later a stimulatory effect on osteoclastogenesis (at doses > 1µM) *via* the OPG/RANK/RANKL system [33, 34]. Disruption of COX-2 gene expression and PGE2 results in defective osteoblast secretion of RANKL and impaired osteoclast formation, with more

pronounced effects of PGE2 on osteoclasts when they were grown in coculture with osteoblasts [20, 36].

Up-regulation of RANKL expression and down-regulation of OPG expression by osteoblasts are involved in the initial osteolytic phase of PCa bone metastases where OPG decreased production is a crucial event for the induction of osteoclastogenesis and the osteolytic microenvironment [20, 32, 37].

Neutralization of PGE2 by specific antagonists, blocking the interaction between PGE2 and its receptors in prostate cancer, may directly suppress cell differentiation into osteoclasts and osteolysis in a xenograft model of osteolytic bone metastasis [9].

Effects of PGE2 on Wnt signaling pathway

The Wnt signaling pathway is involved in embryogenesis (including gastrulation, somitogenesis, and organogenesis), cancerogenesis, and recent research underlines its key role in bone development and growth [30, 38, 39]. The absence of Wnt signaling results in a marked increase in the number of osteoclasts, decreased osteoprotegerin, and severe osteoporosis; increased signaling causes a decreased number of osteoclasts, increased osteoprotegerin, and massively high bone mass [40].

PGE2 modulates the Wnt signaling pathway, bone formation, and prostate cancer bone metastases [9, 41, 42]. Administration of cyclooxygenase (COX) inhibitors and specific antagonists of PG receptors suppresses bone metastasis in prostate cancer cells [9, 43]. PGE2 can directly regulate and activate Wnt activity physiologically through cAMP/PKA-mediated regulation of β-catenin protein stability *in vivo*, promoting its availability for transcriptional activation [41, 44]. PGE2 stimulate canonical Wnt signaling also in neoplastic cell lines and downstream signals as GSK-3β phosphorylation, β-catenin nuclear translocation [42, 44]. In prostate cancer, a high-dose of PGE2 (5–10 µM) increased the expression of Dkk-1 and sFRP, which are two potent Wnt inhibitors predominant in the osteolytic phase of PCa bone metastases. Low dose of PGE2 (0.1 µM) stimulate preosteoblast cell growth, differentiation and Wnt signaling causing the expression of the LRP5/6 Wnt co-receptor, β-catenin, as well as EP1 and EP4 receptors [20].

DISCUSSION

Bone is one of the most preferential sites for metastasis of prostate cancer. Clinical and *in vitro* study suggested a close association between the PGE2 pathways and bone regulation in prostate cancer. The prostaglandin E2, principal metabolic product

of COX2, is a physiological regulator of bone metabolism and remodeling, particularly a potent stimulator of osteoblast differentiation [23, 34, 45, 46].

The aberrant expression of PGE2, affect multiple pathways of bone formation and remodeling in prostate cancer. Imbalances in the bone remodeling process result in metabolic bone diseases characterized either by increased bone resorption (osteolytic bone metastases) or increased osteoblastic bone formation (prostate cancer-induced osteoblastic metastases) [20] (Fig. 2). PGE2 induces both increased osteoclastogenesis and osteoblastogenesis and can promote bone formation and resorption with catabolic or anabolic function [45, 47]. Continuous PGE2 administration stimulate bone catabolism while intermittent exposure led to bone anabolism as the result of imbalance in bone gain over loss with stimulation of endosteal bone formation [48].

In the present review, we report that high doses of PGE2 are very important in the initial osteolytic phase of PCa bone metastases, promoting osteoclast activation trough induction of RANKL in osteoblasts. In contrast, in more advanced osteoblastic phase of prostate cancer bone metastases, low dose of PGE2 can promote osteoblastogenesis activating Wnt pathway. The bone phenotype in prostate cancer also may depend on dose-dependent effects of COX2/PGE2 system on RANK/RANKL/OPG and Wnt pathways.

In the early, osteolytic phase of PCa bone metastases, PCa cells produce high concentration of PGE2 which increased expression of both Dkk-1 and sFRP, inhibitors of Wnt. Activated osteoclasts secrete high concentration of PGE2 that can increase Wnt-inhibitor expression by both PCa and osteoblast-lineage cells. In osteoblastic phase of PCa bone metastases low secreted levels of PGE2 promote Wnt-activated osteoblastogenesis. Consequently in this phase COX-2 inhibitors may be harmful.

Neutralization of PGE2 or its receptors by specific antagonists may directly suppress cell differentiation into osteoclasts and induction of RANKL in osteoblasts in the initial osteolytic phase of PCa bone metastases. Inhibition of PGE2 effectors such as Wnt/ β -catenin pathway can prevents osteoblastic bone metastases in more advanced osteoblastic phase.

CONCLUSIONS

Recent literature analyses outline the biologic relevance of PGE2 for the bone metabolism and remodeling under both physiologic and pathologic conditions.

PGE2 has a biphasic effect on bone metabolism mediated by different and specific pathways on prostate cancer cell. The balance between specific anabolic and catabolic mechanisms of PGE2 system, dose-dependent and receptor-specific, seems to be a promising strategy for future therapy. Our finding suggests that PGE2 act as a regulator in maintaining normal bone mass and micro-architecture and indicate a mechanism whereby chemical manipulation of PGE2 levels or signaling may be therapeutically beneficial for the controlled regulation of both bone pathology and cancer treatment in prostate neoplasm.

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