The dual face of parathyroid hormone and prostaglandins in the osteoimmune system

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Agas D, Marchetti L, Capitani M, Sabbieti MG. The dual face of parathyroid hormone and prostaglandins in the osteoimmune system. Am J Physiol Endocrinol Metab 305: E1185–E1194, 2013. First published September 17, 2013; doi:10.1152/ajpendo.00290.2013.—The microenvironment of bone marrow, an extraordinarily heterogeneous and dynamic system, is populated by bone and immune cells, and its functional dimension has been at the forefront of recent studies in the field of osteoimmunology. The interaction of both marrow niches supports self-renewal, differentiation, and homing of the hematopoietic stem cells and provides the essential regulatory molecules for osteoblast and osteoclast homeostasis. Impaired signaling within the niches results in a pathological tableau and enhances disease, including osteoporosis and arthritis, or the rejection of hematopoietic stem cell transplants. Discovering the anabolic players that control these mechanisms has become warranted. In this review, we focus on parathyroid hormone (PTH) and prostaglandins (PGs), potent molecular mediators, both of which carry out a multitude of functions, particularly in bone lining cells and T cells. These two regulators proved to be promising therapeutic agents when strictly clinical protocols on dose treatments were applied.

osteoinmunology; bone; parathyroid hormone; prostaglandins; immune system

MESENCHYMAL STEM CELLS (MSCs) and hematopoietic stem cells (HSCs) reside within the bone marrow, which provides structures and molecular components for their homing, support of their various functions and states of differentiation, self-renewal, and quiescence. Several authors agree that HSCs are localized near the endosteal surface, albeit not exclusively adjacent to osteoblastic cells, probably with distinct distance-dependent functions in the skeletal and immune systems (47, 58, 144). Likewise, recent findings revealed that mesenchymal progenitors residing in endosteal bone marrow adjacent to the sites of bone formation (such as trabecular bone and endostea) behave differently than those in the central bone marrow (108). The bone marrow niches perform a fine-tuned sorting of molecular signals that control bone and hematopoietic cell homeostasis. Bone microenvironment is characterized by the elegant poise between osteoblasts and osteoclasts in a multifaceted bone remodeling process which occurs predominantly at the cancellous and endosteal surfaces in close proximity to the bone marrow. The current findings concur that osteoblasts are recruited in distinct areas called “basic multicellular units” by osteoclasts via cross-talk between both cell types and begin to lay down new bone matrices (14, 25). This complex and dynamic equilibrium of bone cells is regulated by several systemic factors, such as bone morphogenetic proteins (68, 97, 102, 146), parathyroid hormone (PTH) (39, 73, 100), and prostaglandins (PGs) (3, 4, 99, 101), as well as shared cytokines, transcription factors, and membrane receptors in the immune and skeletal systems (49, 123). Modern research has argued that these two systems interact with each other and that impaired cross-talk between the distinct niches in the marrow creates pathological conditions like chronic inflammatory joint diseases, known as rheumatoid arthritis (RA) (27, 38) and chronic arthritis (16), which lead to decreased bone density and alter the mechanical properties of the bone itself. Accumulating evidence has continuously reinforced the thesis that both innate and adaptive immune cells contribute to the differentiation of MSCs and to the maturation of osteoblasts and osteoclasts through the secretion of specific mediators (49, 87). Within the bone marrow microenvironment, the osteoblasts lining the endosteal surface of the trabecular bone could provide primary support for HSC differentiation (76, 87) and the osteoclastogenesis (36, 121). Osteoblasts synthesize a number of cytokines that contribute to the support and regulation of HSCs by the endosteal niche. The osteoblastic lining cells produce angiopoietin-1 (Ang-1), which sequentially stimulates the HSCs to produce the specific receptor for Ang-1 (Tie-2 tyrosine chinasine kinase receptor) that binds the HSCs to the trabecular bone lining cells (7, 152). The Ang-1/Tie-2 complex also provides significant signals for the maintenance of the long-term repopulating (LTR)-HSCs and of LTR-HSCs stemness (140) while affecting the differentiation capacity of hematopoietic lineages during development (45).

A fine study performed by Visnjic et al. (133) has demonstrated the linkage of bone marrow hematopoiesis to osteoblasts via an osteoblast-killing compound, ganciclovir. The selective ganciclovir-induced loss of osteoblasts caused a progressive loss of bone, loss of bone marrow cellularity, and loss...
of early hematopoietic progenitors. When treatment was stopped, hematopoiesis returned to the bones as osteoblasts reappeared, along with pockets of hematopoiesis at sites of new bone formation (133, 142). It was also noticed that N-cadherin interaction between hematopoietic cells and osteoblasts plays a key role in the maintenance of the HSC phenotype (150). However, more recently, evidence was shown that HSC expansion is not affected by a decrease in osteoblasts (42).

In turn, osteoblast-mediated bone formation is influenced by cytokines in the immune system, and targeted disruption of immunomodulatory molecules resulted in unforeseen phenotypes in the skeletal system (123).

Furthermore, it is widely acknowledged that osteoclast differentiation is controlled by factors such as the macrophage colony stimulating factor (M-CSF) and the receptor activator NF-κB (RANK) ligand (RANKL) produced by both osteoblasts and T cells. These factors act as regulators of osteoclastogenesis, and RANKL has been characterized as one of the most important molecules that unequivocally connects the bone and immune systems (123). In line with this, the inhibition of osteoclast activity by strontium impedes the hematopoietic engraftment in mice receiving bone marrow transplantation, underlining the ability of osteoclasts as potential HSC regulators (60). A different bone marrow macrophage subpopulation, the OsteoMacs, plays an opposite role in bone remodeling by allowing osteoblasts to survive and providing HSC homing. The OsteoMacs are intercalated within murine and human osteal tissues, and their depletion causes a complete loss of the osteoblast bone-forming surface (143). The above considerations predict an interplay of different molecules in bone marrow niches that preferentially affects a subset of multipotent progenitors, eventually leading to the reciprocal co-evolution, through cytokine secretion, of populations of HSCs and osteoblasts (42).

Molecular Mediators Within the Niches

The “niche” concept was first proposed by Schofield (105) during the late 1970s and suggested that HSCs require the support of other cell types in the bone marrow to maintain HSC potency. Today, it has been widely demonstrated that the niches play important roles in regulating the behavior of the skeletal and immune systems with respect to homeostasis and responses to exogenous stress.

As cited previously, the Ang-1/Tie-2 complex signals maintain adherence of the HSCs to the osteoblastic-lining cells, preserve HSCs from apoptotic stimuli, and preserve the HSCs’ ability to proliferate transit-amplifying progenitors, which generate promptly once required (7, 142). Although Ang-1/Tie-2 signaling has been described as playing a key role in the interaction between the niches (142), there are numerous molecules involved in hematopoietic and bone cell homing, proliferation, and differentiation.

In bone, the RANKL protein [investigated extensively by Takayanagi (123) and Souda et al. (115)] is expressed by osteoclastogenesis-supporting cells and osteoblasts in response to osteoclastogenic factors such as 1,25-dihydroxyvitamin D3, prostaglandin E2 (PGE2), and PTH. Namely, osteoblasts produce RANKL, which by binding to its receptor promotes maturation, differentiation, and activation of osteoclasts. Also, the secretion of RANKL by monocytes, neutrophils, dendritic cells, and B and T lymphocytes underscores the involvement of the immune cells in osteoclastogenesis. The proinflammatory cytokines produced by the hematopoietic population, such as tumor nuclear factor-α (TNFα) and interleukin (IL)-1, IL-3, IL-6, IL-7, IL-11, IL-15, and IL-17, increase osteoclast differentiation and functions (16, 38, 110). Furthermore, specific ILs have been considered important accelerators of bone destruction in RA (111, 123). Conversely, cytokines such as interferon (IFN)α, IFNβ, IFNγ, IL-4, IL-5, IL-10, IL-12, IL-13, and IL-18, produced by helper T (Th) subset T cells Th1 and Th2, exert inhibitory effects on osteoclastogenesis (16, 23, 123). In addition, distinct ILs moderate the action of the exclusive osteoclastogenic T cell subset Th17 blocking IL-17 release (103) with consequent decreased bone resorption and joint inflammation in a RA context (136). Moreover, the regulatory T cells, another T cell subpopulation, are also characterized by their anti-inflammatory and antiosteoclastogenic properties through secretion of IL-4, IL-10, and transforming growth factor-β (TGFβ) (9, 53). Although some authors have argued that TGFβ promotes osteoclast differentiation (95), this growth factor is widely related to the stage-dependent proliferation and maturation of the osteoblastic line (6, 62, 90, 128). In particular, TGFβ was demonstrated to induce osteoprotegerin (OPG) production, a bone-protective agent of the TNF receptor superfamily expressed ubiquitously in several tissues (51). OPG acts as a decoy receptor since it binds to RANKL, avoiding RANKL interaction with its receptor RANK, which is expressed by osteoclast precursors, eventually leading to the inhibition of osteoclastogenesis since the RANKL/RANK pathway is not triggered (74, 79). Regarding the maintenance of immune tolerance, TGFβ induces lymphocyte proliferation, differentiation, and survival, and its disruption leads to pathological conditions such as autoimmune diseases, inflammation, and cancer (65, 107). TGFβ interacts with other critical factors in the bone marrow niche like PTH and PGs controlling bone marrow stromal cells (BMSCs) and HSCs homeostasis. Qin et al. (89) demonstrated that PTH on the one hand enhances bone formation through a TGFβ-mediated type I collagen production mechanism and on the other stimulates the RANKL expression and simultaneous inhibition of OPG. A remarkable study by Calvi et al. (17) showed that PTH-treated stromal cultures increased the number of osteoblasts and their ability to support hematopoietic cells in a PTH-dependent niche. Another in vivo study by Adams et al. (2) has revealed that systemic intermittent treatment with PTH expanded the HSC niche. Furthermore, it is well documented that PTH is one of the principal stimulators of PGE2 in osteoblasts, and PGE2 may act as a local mediator of the HSC niche (59, 127). Thus, locally produced PGE2 could mediate the effects of PTH-dependent HSC expansion through niche activation (87); subsequently, T and B cells interact with BMSCs and bone cells in a complex cross-talk scenario of bone remodeling and lymphocyte maturation in the marrow microenvironment. These two regulators have also been characterized as double-edged swords for their different dose/niche maturation-stage effects. Although numerous factors and interactions have to be considered, the comprehension of how PTH and PGs exert their
action on the osteoimmune system could provide regulatory inputs and new therapeutic platforms for bone and immune disorders comprising bone marrow transplantation engraftment strategies.

**PTH Outcomes: Exploring “The Bright and the Dark Side of the Force”**

General concepts. PTH is an 84-amino acid peptide [PTH-(1–84)] that, together with its active fragments, exerts contrasting effects on bone. PTH binds to the PTH type 1 receptor, a class II G protein-coupled receptor, and activates classic G protein signaling pathways such as the phospholipase C (PLC)-β and protein chinase C pathway (48, 73). The PTH action on the skeletal system is complex since this hormone enhances both osteoblast-dependent bone formation and osteoclast-dependent bone resorption.

“Anabolic” bone-building effects were observed after brief exposures to PTH; indeed, intermittent daily administration of PTH promotes bone formation through a marked increase in trabecular bone volume due to a preponderant stimulation of trabecular bone formation and also causes a small loss of cortical bone (48, 73, 96). Several authors have demonstrated the PTH’s effects in altering the osteoblastic pool and driving mesenchymal stem cells to differentiate into osteoblasts both in vitro and in vivo (20, 46). Likewise, we have shown that PTH treatment in vitro increases osteoblast survival and differentiation based on time and dose. Fibroblast growth factor-2 (FGF-2) plays a part in these effects (100). In point of fact, intermittent PTH administration is an approved treatment modality for osteoporosis (18, 73). Indeed, the recombinant native human hormone [rhPTH-(1–84); Preose] and the two fragments/analogs [hPTH-(1–34); Forteo] and [Leu27)cycl(Glu22-H9252

Subcutaneous injections of purified native bovine PTH restored the hematopoietic cell subpopulations (94). In addition, the ability of the HSCs to sense ambient calcium has been well documented as of the 1980s, and it is a crucial factor for their homing and retention with respect to bone marrow. Silver et al. (109) demonstrated that HSCs express the calcium-sensing receptor (CaR), which is indispensable for niche spatial localization, and more recently, Adams et al. (1) revealed that CaR is indispensable for the proper engraftment of HSCs within the endosteal niche that is rich in extracellular calcium. In addition, genetic deletion of CaR reduced PTH-stimulated bone turnover in trabecular bone and tended to impede PTH-induced increases in trabecular bone (145). Under normal physiological conditions, PTH plays a watchdog role for calcium homeostasis, and, further, PTH treatment provides stromal support for primitive hematopoietic cells (17, 49). Within bone marrow, the presence of HSCs in proximity to the endosteal surface of bone also suggested a possible role of the HSC niche in osteoblast metabolism (2, 54, 76, 119). Osteoblasts produce hematopoietic growth factors in a PTH-related process or the locally produced PTH-related protein (PTHrP) through the PTH/PTHrP receptor (119).

Calvi et al. (17) showed that the constitutively active form of the PTH/PTHrP receptor expressed in osteoblasts of transgenic mice, despite the trabecular number and the trabecular osteoblasts of the long bones being increased, leads to a specific expansion of the HSCs through a Notch-dependent mechanism. Notch signaling involves membrane-bound ligands and has been defined as a potent modulator of HSC self-renewal (50, 80, 87). Still, it is acknowledged that Notch activation and cytokine receptor signaling exert synergistic effects on hematopoietic cells (132). Intermittent administration of PTH on mice increased Notch ligand Jagged1 in trabecular and endosteal osteoblasts and spindle-shaped cells in the bone marrow microenvironment (137). The consequent activation of the PTH receptor (PTHrP) in osteoblasts, which reflects increased Jagged1 and Notch signaling in HSCs, preserved the self-renewal capacity of the hematopoietic niche and safeguarded stem cell homeostasis. The molecular mechanisms involved in the PTH action on Notch signaling in bone and immune components are under wide-ranging investigation also for their controversial role in the niches. Although in vitro Notch receptor studies failed to correlate Notch signaling to HSC differentiation (15, 131), several authors have suggested that both niches express Notch ligands, and therefore, receptors (63, 64, 87) can exert mutual responses. Accordingly, PTH facilitates LTR-HSCs stemness and HSC bone-lining cell interactions by attenuating Jagged1/Notch proteins, Ang-1/Tie-2-induced β1-integrin and N-cadherin expression, and Wnt signaling (17, 24). The Wnt molecular cascade, barring its interactions by attenuating Jagged1/Notch proteins, Ang-1/Tie-2-induced β1-integrin and N-cadherin expression, and Wnt signaling (17, 24). The Wnt molecular cascade, barring its ability to drive HSC self-renewal, could also reprogram osteoblast differentiation and enhance the capacity of osteoblasts to support HSCs (87). The clinical relevance of these findings reflects the fact that PTH-dependent HSC expansion dramatically improves the survival of mice receiving bone marrow transplants (17). As noted by Whitfield (142), PTH may become a valuable marrow-stimulating tool for safely promoting the engraftment of peripherally harvested HSCs in cancer patients. An additional aspect is that it has been observed that T cells can regulate bone homeostasis through the secretion of pro- and antiosteoclastogenic factors and unfolds; this is a
further, definitive role of these cells as mediators of the PTH bone-remodeling effects (21, 30, 139). Moreover, activated T cells express surface receptors that bind to and activate counterreceptors found on the osteoblast surface. An example is the CD40L T cell receptor, which upon ligation to stromal cells and osteoblasts expressed CD40, which provides survival signals in both cell types (5). Additionally, T cells help osteoblasts to support osteoclastogenesis by increasing the bone marrow MSC differentiation into the osteoblastic line and thus enhance the production of osteoclastogenic cytokines from the above niches (30, 93). In this context, T lymphocytes became significant moderators of MSCs and osteoblasts to support PTH-induced osteoclastogenesis. It is worth mentioning that the regulatory effects produced by either CD4+ or CD8+ T cells are extended to the regulation of RANKL/OPG production from osteoblasts or stromal mesenchymal stem cells. As a consequence, these T cells support PTH-osteoclastogenic effects through CD40L/CD40 signaling (30). The lack of T cells abrogates the capacity of PTH to stimulate bone resorption but not bone formation; furthermore, it has been shown that PTH can cause a greater increase in trabecular bone volume in T cell-deficient animals than in T cell-repleted mice (30). As a result, PTH, in the presence of T cells, contributes to the osteoclastogenesis, which is an indispensable passageway for the bone remodeling process.

In a more recent study, Terauchi et al. (126) observed that intermittent PTH treatment increases the production of Wnt10b by bone marrow CD8+ T cells, resulting in the activation of Wnt signaling in preosteoblasts. The activation of Wnt signaling plays a relevant role in intermittent PTH-induced bone anabolism. The Wnt ligands Wnt10b, Wnt7a, and Wnt3b switch on signaling events related to osteoblast proliferation, differentiation, and OPG production (12, 13, 57). Thus, CD8+ T cell/Wnt10b production under intermittent PTH stimulation indicates an important T cell feature in PTH-induced bone strength. In class I MHC−/− mice, the anabolic PTH/bone effect was abrogated, highlighting the importance of T cells in trabecular bone formation (126). Furthermore, it is acknowledged that osteoblast-specific overexpression of the Wnt inhibitor DKK1 or WIF caused an impaired HSC self-renewal (26, 104). These findings revealed tantalizing scenarios regarding the involvement of different niches controlling PTH effects on trabecular bone resorption/formation and on HSC homing. It has to be underscored that the effects of PTH on bone homeostasis are multilateral and in pathological conditions (i.e., inflammatory arthritis) are influenced by either genetic background or the stage of the disease. As regards this aspect, Young et al. (148) found that Th2 cell-derived PTH acted as a cytokine for local cell communication instead of as a hormone and calcium homeostasis regulator; indeed, PTH expression in Th2 cells was not regulated by extracellular Ca2+ concentrations. Interestingly, Th2 cell-derived PTH maintains a basal level of alkaline phosphatase (ALP) activity of primary osteoblasts, although the expression of bone matrix proteins, although useful for the late stage of osteoblast maturation, was not significantly influenced. In addition, the Th2 cytokine microenvironment enhanced the expression of RANKL and OPG with a prevalence in OPG production, thus favoring the anabolic activity of the osteoblasts (148). On the other hand, the same authors found that Th1 cells inhibited ALP activity through an IFNγ mechanism and shifted the balance of bone remodeling toward bone loss. These observations indicate the importance of the cytokine environment, formed by Th1 and Th2 cells, in bone homeostasis. Taking into account that PTH can exert dose- and time-dependent catabolic effects on bone and that Th2 cell-derived PTH upregulates RANKL expression, Young et al. (148) questioned the possibility that the hormone production could potentially stimulate overactive bone remodeling and increase bone loss in arthritis. The above observation underscores the signaling network complexity of narrow microenvironment components, especially under inflammatory conditions. The PTH-induced specific molecular mediators within the bone marrow niches are schematized in Fig. 1.

**PGs as Bone Marrow Microenvironment Regulators**

**General concepts.** PGs are a group of lipid mediators that play distinct roles as regulators of homeostasis and inflammation. These molecules are synthesized by a conserved biosynthetic pathway controlled via specific enzymatic steps as follows. First, the arachidonic acid, the precursor molecule for prostanooids, is liberated by phospholipase A2s; second, it is converted to PGH2 by either cyclooxygenase 1 (COX-1) or cyclooxygenase 2 (COX-2); third, PGH2, which is a common precursor of all prostanooids, is metabolized to various PGs

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**Fig. 1.** Parathyroid hormone (PTH) effects within the niches. PTH activates numerous cytokines and other mediators on osteoblasts (OBs), osteoclasts (OCs), bone marrow mesenchymal stem cells (MSCs), and hematopoietic stem cells (HSCs) located close to the endosteal niche. These molecular interactions described a complex homeostatic tableau resulting in anabolic or catabolic scenarios for each single niche. PTH administration has controversial spatiotemporal effects in the osteoimmune system correlated to therapeutic protocols applied and the clinical conditions. RANKL, receptor activator NF-κB ligand; ANG-1, angiotensin I; OPG, osteoprotegerin; CaR, calcium-sensing receptor; Th, helper T cells; ALP, alkaline phosphatase.

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**Table: Molecular mediators and Effects within the niches**

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<td>Jagged1/Notch OPG</td>
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<td>CD40L/CD40</td>
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<td>RANKL</td>
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<td>CaR(Ca2+) AnG-1/Tie2</td>
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<td>β1-integrin N-cadherin</td>
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<td>Wnt/β-catenin LTR-stemness/homing</td>
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<td>PTH (as cytokine)</td>
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such as PGE₂, PGD₂, prostaglandin F2α (PGF2α), prostacyclin, and thromboxane by the action of specific PG synthases (130). PGs exert their effects by activating the prostaglandin receptor subfamily, which is composed of eight members: the PGE receptors EP₁, EP₂, EP₃, and EP₄, the PGD receptor DP₁, the PGI receptor (IP), the PGF receptor, and the thromboxane receptor (72). PGs are produced in response to several factors and have been found at elevated levels in synovial fluids, synovial membranes, articular cartilages, and articular bones under pathological conditions. Indeed, both COX isofoms are coexpressed in circulating inflammatory cells ex vivo and in inflamed RA synovium and atherosclerotic plaques (22, 106).

Early studies using COX-2 and PGE₂ receptor knockout mice showed that PGE₂ signals through EP₁ to regulate the Ca²⁺ channel and to EP₃ to inhibit the production of cAMP and adenylyl cyclase via G₁ protein (52, 117). In contrast, EP₂ and EP₄ increase cAMP levels and β-catenin signaling via phosphoinositide 3-kinase or cAMP/PKA (29, 37). Interestingly, Goessling et al. (33) reported that the PGE₂-induced Wnt/β-catenin signaling contributes to hematopoietic stem progenitor cell development and regeneration. More recent studies have also suggested that PGE₂/EP₄ accelerates HSC proliferation and adhesion by activation of the marrow MSCs, which produce mitogenic ligands and cell adhesion molecules (45). EP₂ and EP₄ abrogation mediate development of paw swelling associated with collagen-induced arthritis, and EP₄ appears to play a proinflammatory role in RA (41, 149). On the other hand, EP₄ deletion in bone marrow-derived cells enhanced proinflammatory agent production (124), emphasizing the capacity of PGE₂/EP₄ to exert biphasic effects. Recent findings suggest that a stable PGE₂ derivative, 16,16-dimethyl PGE₂, significantly enhances the engraftment of human cord blood cells within bone marrow in a xenotransplanted model (34), conferring an important therapeutic role to this prostaglandin. Thus far, PGE₂ is able to modulate various processes in a scenario-dependent manner, and its regulatory role in hematopoiesis has been well documented for more than three decades (83, 84). Concerning the osteoblast/osteoclast metabolism, we and others showed that PGs such as PGE₂ and PGF₂α exert both stimulatory and inhibitory effects on bone formation in cell and organ culture (3, 4, 91, 92, 99, 101), acting in an autocrine and/or paracrine manner (86). Suda et al. (115) have also reported that IL-6 can stimulate osteoblasts to induce RANKL expression through a PGE₂-related mechanism and, consequently, osteoclastogenesis. PGD₂ also participates in multiple physiological and pathological conditions, including bone metabolism, and exerts anti-inflammatory effects in several models of inflammation (32).

**PG action within the niches.** HSC self-renewal and differentiation are controlled by microenvironmental signals within bone marrow that establish an interchange circuit between the osteoblastic cells and the hematopoietic niche. Early studies showed that PGE₂ is able to stimulate proliferation, cycling, and differentiation of quiescent bone marrow cells into colony-forming cells and participates in hematopoiesis and myelopoiesis regulation (31, 83, 85). Most recent concepts indicated that PGE₂ can target both stromal mesenchymal cells and hematopoietic components. The ex vivo exposure of bone marrow cells to PGE₂ facilitates murine hematopoietic cell engraftment (78). Moreover, in vivo treatment with PGE₂ expands HSCs in the absence of injury and accelerates hematopoietic recovery after stem cell transplantation (28, 40). Interestingly, Hoggatt et al. (40) demonstrated that PGE₂ has direct, stable effects on LTR-HSCs and facilitates HSC engraftment through upregulation of the chemokine receptor CXCR4. In light of this, osteoblastic cells produce the stroma-derived factor 1 (SDF1; or CXCL12) that directs HSC localization. The SDF1-CXCR4 axis is considered the best-defined regulator of HSC homing in bone marrow (58, 144). Keeping in mind that SDF1 function is controlled by integrins (82) and that integrins α4β₁, α₁β₁, and α5β₁ facilitate HSC retention and localization within the bone marrow niches (77, 88), it should be intriguing to consider the PGE₂ effects on these adhesion molecules. Likewise, future studies on other mediators of the osteoblast-derived extracellular matrix proteins like the SPP1 protein, which influence HSCs population, appear to be mandatory.

Additionally, PGE₂ treatment enhanced expression of survivin, a protein with antiapoptotic action in the HSC niche, and increased the proportion of LTR-HSCs entering into and progressing through the cell cycle. Hoggatt et al. (40) argued that the PGE₂-enhanced HSC survival corresponds to either enhanced engraftment within the marrow microenvironment or enhanced migration. Contemporaneously, Frisch et al. (28) have shown that in vivo PGE₂ treatment exerts a significant effect on short-term HSCs without excluding a smaller effect on LTR-HSCs. Moreover, they observed a disruption of the trabecular bone microarchitecture that possibly reflects an active PGE₂-dependent remodeling process. These authors concluded that PGE₂ might be a local mediator and/or an amplifier of PTH effects on the bone marrow microenvironment. The ST-HSC expansion and trabecular bone architecture modifications highlighted the involvement of PGE₂ in both niches (28).

The discrepancy of the above findings on PGE₂’s effects on LTR-HSCs and short-term HSCs could be due to the protocol regimen used for the in vivo studies. Although the clinical relevance of these data regarding the hematopoietic recovery after chemotherapy or stem cells transplantation is noteworthy, a spontaneous observation about PGE₂’s effects on bone homeostasis is warranted. PGE₂ can exert dose/time-dependent dissimilar effects on trabecular net or at periosteum levels, suggesting that it acts as a mediator between bone deposition or bone disruption. Thus, an in depth examination of the possible “double-barrelled” action of PGE₂ within the niches becomes essential.

Furthermore, PGE₂ can operate as a T cell immunosuppressor or T cell immunostimulator in a dose-dependent scenario that also involves EP₂ and EP₄ receptors. The PGE₂-immunosuppressive effect was correlated with IL-2 and IFNγ inhibition (T₈₁). Therefore, it was stated that PGE₂ might modify T₈₁ cell polarization, suggesting a specific role in controlling T₈₁/T₁₂ balance (11, 112). Taking into account that IFNγ strongly inhibits osteoclastogenesis and that normal T₈₁ functions prevent bone loss (122), it is deductible that PGE₂-dependent T₈₁ abrogation results in impaired bone turnover. Conversely, nanomolar or micromolar concentrations of PGE₂ enhanced T₁₂ and T₁₇ differentiation in a proinflammatory context (71, 147). T₁₇, as the exclusive osteoclastogenic T cell subset, releases IL-17-induced RANKL on mesenchymal cells (55) associated with inflammation and bone destruction. The poten-
Fig. 2. Prostaglandin (PG) effects within the niches. PGS signal in the bone marrow microenvironment, affecting a subset of downstream molecular cascades. PGS activate cytokines, growth factors, receptors, and transcription factors into the niches to regulate the turnover and the behavior of bone and hematopoietic cells. In particular, prostaglandin E2 (PGE2) and prostaglandin 2α (PGF2α) can exert both inhibitory and stimulatory effects related to the differentiation stage of the single niche or with impaired metabolic functions.

Concluding Remarks and Perspectives

The study of the cross-talk mechanisms between skeletal and immune systems has opened the “bag of Aeolus,” and the potential clinical applications are at the door. It is well documented that osteoblastic cells can support terminal granulopoiesis and HSC survival in vitro (118), expand HSCs in vitro (120), and produce important factors for HSC homing (118). In addition, osteoblastic cells engraft HSCs during bone marrow transplantation, and their cotransplantation with HSCs may increase engraftment rate (75). On the flip side of the coin, T cells increase the capacity of stromal MSCs to support PTH-induced osteoclastogenesis (30) and trabecular bone formation (126). These fascinating considerations in osteoimmunology are being applied for the development of new therapeutic platforms against osteoporosis and inflammatory arthritis and in marrow transplantation techniques. Data concerning the signal transduction mechanism of the effects of PTH and PGs within the niches provide extra criteria for the specific manipulation of the bone marrow microenvironment. Although the distinct functions of the niches tend to converge toward a complex physiological homeostatic tableau, several cues have underscored the twofold action of significant players. Specifically, the results produced with PTH and PGs are, in some cases, contradictory depending on the treatment protocol and the normal or pathological clinical profile of administration. A critical challenge for the understanding of the molecular interactions within bone marrow niches will be the in-depth analysis of the PTH and PGs’ involvement in the complex bone marrow microenvironment. For example, the synergistic dose-dependent effects of PTH/PGE2, PTH/PGF2α, or PTH/FGF-2, combined with gene therapy approaches, could provide useful outcomes for bone regeneration, skeletal disorders, and HSC engraftment after transplantation.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

D.A. and M.G.S. contributed to the conception and design of the research; D.A. and M.C. analyzed the data; D.A. prepared the figures; D.A. and M.G.S. drafted the manuscript; D.A., L.M., M.C., and M.G.S. edited and revised the manuscript; D.A., L.M., M.C., and M.G.S. approved the final version of the manuscript; M.G.S. performed the experiments.
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