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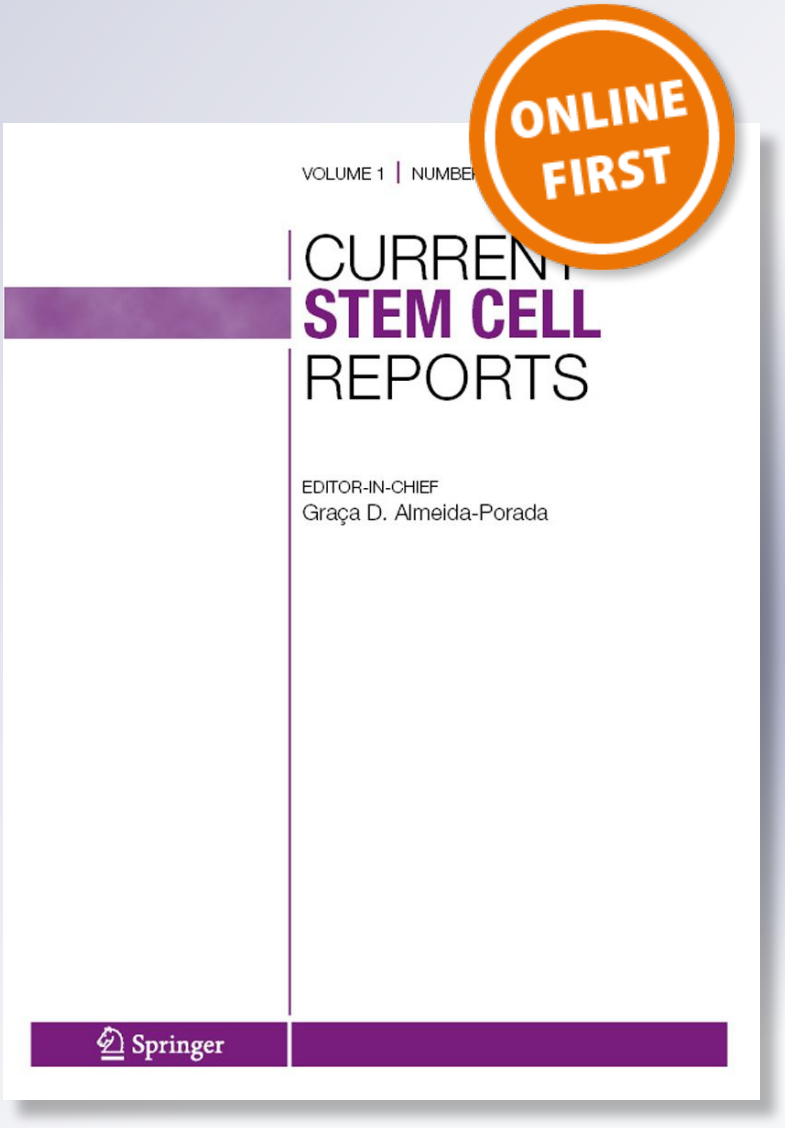
Current Stem Cell Reports

e-ISSN 2198-7866

Curr Stem Cell Rep
DOI 10.1007/s40778-017-0091-7



Springer

Curr Stem Cell Rep
DOI 10.1007/s40778-017-0091-7

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CELL:CELL INTERACTIONS IN STEM CELL MAINTENANCE (D BONNET, SECTION EDITOR)

Role of PTH in Bone Marrow Niche and HSC Regulation

Maria Giovanna Sabbieti[1] · **Luigi Marchetti**[1] · **Roberta Censi**[2] · **Giovanna Lacava**[1] · **Dimitrios Agas**[1]

Abstract
Purpose of Review The bone marrow microenvironment hosts a multicellular complex that is extraordinary in its interdependence and function. The composite machinery within the axial and long bones is involved in the homing, maintenance, differentiation, and egress of hematopoietic/progenitors stem cells (HSCS) as well as mesenchymal/stromal stem cells (MSCs) that dwell in specific anatomical areas inside the marrow space, described as niches. The need for more efficient hematopoietic stem cell transplantation protocols and bone marrow manipulation techniques has motivated scientists to identify effective niche regulators such as the parathyroid hormone (PTH).
Recent Findings PTH treatment is increasingly used with promising outcomes in autologous and allogeneic transplantation of HSCs, because PTH operates as a significant mediator in HSC engraftment, expansion, and mobilization. In addition to the well-established anti-osteoporotic effect of PTH, there is evidence that it may also coordinate hematopoietic stem cell activities.
Summary This report provides up-to-date information about PTH action within marrow niches and highlights the importance of this hormone in the behavior of hematopoietic elements in the bone marrow.

This article is part of the Topical Collection on *Cell:Cell Interactions in Stem Cell Maintenance*

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Published online: 10 July 2017

Keywords PTH · PTHrP · Bone marrow niche · Hematopoiesis · HSCs

Introduction: the Current Understanding of Bone Marrow Structure and Function

The structure and function of the bone marrow have been the object of scientific research for many decades. Certainly, the study of the elegant equilibrium between the different habitats of the bone marrow reservoir presents a complex challenge. Specialized cellular compartments within the bone cavities are characterized by interdependence and interconnectedness and establish dynamic operational microareas designated as niches. The niche milieu encompasses a panorama of undifferentiated and stem elements as well as mature cells. The niche hosts mesenchymal/stromal stem cells (MSCs) many of which can commit to form osteoblasts, chondrocytes, and adipocytes and hematopoietic stem/progenitor components (HSCs) which give rise to blood cells. In particular, the primitive murine hematopoietic cells have been identified as a heterogeneous Lin^-, $Sca1^+$, and $C\text{-}kit^+$ (LSK) population comprising multipotent progenitors (MPP), long-term HSCs (LT-HSCs), and short-term HSCs (ST-HSCs) [1, 2].

The niche ontogeny is complemented by various space-specific resident cells, such as perivascular reticular cells, perivascular mesenchyme progenitors, endothelial cells, and neuronal and muscle stem cells, which actively participate in the microenvironmental homeostasis [2]. Current findings indicate that some HSCs are located near the endosteal bone surface (endosteal niche) with distinct functions that are dependent on the distance from the bone surface while others are in close proximity to the specialized blood vessels within the bone marrow, the sinusoids (vascular niche) [3–5]. Both the endosteal and the sinusoidal regions are strategic bone marrow

areas that support HSC maintenance, self-renewal, quiescence, differentiation, and egression. These features are made possible by the involvement of additional factors including cytokines and hormones, which are critical for the bone marrow homeostatic tableau.

The Interdependence of Niche Inhabitants

Accumulating evidence indicates that the "bone forming" osteoblasts, the "bone feeder" osteoclasts, and the MSCs are the foremost regulators of the HSC phenotype. The wide array of MSC functional and architectural properties provides the required platform for the assembly and organization of the skeletal and perivascular hematopoietic niche framework within the bone marrow. For this reason, MSCs and progenies have been considered for about two decades the preeminent niche manufacturers [2]. In point of fact, it is thought that the different committed MSCs progenies provide signals for HSC differentiation and osteoclastogenesis [6, 7], while the in vivo depletion or impaired function of osteoblasts in mice disrupts hematopoiesis. In accordance, the osteocalcin^{+} osteoblasts have been identified as HSC-supporting cells because immature hematopoietic cells were found organized in follicle-like structures next to them [3]. Moreover, it has been found that HSCs establish contacts with osteoblasts lining the bone surface, named spindle-shaped N-cadherin^{+}CD45^{-} osteoblastic (SNO) cells, which express high levels of the multifunction N-cadherin protein. N-cadherin-mediated interaction between osteoblasts and hematopoietic cells plays a critical role in the survival and homing of HSCs and hematopoietic progenitors [3]. In addition, tunica endothelial cell kinase 2 receptor (Tie2)/angiopoietin-1 (Ang-1) signaling supports tight adhesion of HSCs to the niche through an N-cadherin/β1-integrin-dependent mechanism [8]. Taking into consideration the complexity of the niche morphology, these precedent studies have deduced that both the osteoblasts and the endosteal niche are key components of HSC maintenance [9–11]. On the contrary, modern concepts argued that osteoblasts create a niche for certain early lymphoid progenitors but not for HSCs [12••]. Specifically, deletion of SCF, CXCL-12, and angiopoietin using Col2.3-Cre ablation of osteoblasts in mice does not affect the HSC function and the overall HSC numbers but impaired LT-self-renewal of HSCs [12, 13••, 14–17].

In this view, other findings indicated that HSCs depend on a perivascular niche created by endothelial cells and leptin receptor (Lepr)- or Prx1-expressing perivascular stromal cells, whereas osteoblastic cells and endosteal niche support proliferation and differentiation of some early lymphoid progenitors [12••].

Likewise, at least three studies have provided evidence highlighting the contribution of the vascular niche: in one study, human MSCs expressing CD146 proved capable of supporting HSCs at the sinusoidal level [18]. Two other studies reported that MSC subpopulations within the same compartment, such as CXCL12-abundant reticular (CAR) cells, orchestrate HSC metabolism via stem cell factor (SCF) and CXCL12 production [19, 20]. In addition, in vivo depletion of the MSC pool expressing the intermediate filament nestin reduces bone marrow homing of HSCs, an indication that = nestin^{+} MSCs are important HSC regulators [21].

The distinct bone marrow anatomical zones and their topographical interactions continue to be the subject of controversy. Several authors suggested that the endosteal niche maintains HSC quiescence [3, 5, 8], whereas the vascular niche supports stem and progenitor cell homeostasis and regulates megakaryopoiesis [4]. However, current findings have indicated quite the opposite, reporting that HSCs reside adjacent to the perivascular niche, whereas early lymphoid progenitors inhabit the endosteal area [12••]. The multifaceted bone marrow microarchitecture and the candidate anatomical microareas for the HSCs continue to be the object of intense investigation.

Bone Deposition is Controlled by Niche Elements

Bone formation and osteoblast physiology are influenced by the metabolic features of HSCs [22]. Stem, progenitor, and mature hematopoietic cells coordinate bone cell differentiation and matrix deposition. For instance, osteomacs, a specific macrophage subdivision, provide bone-forming signals during the deposition phase [2].

The physical interactions between the niches, and consequently the fate of the MSCs and HSCs, are broadly influenced by a plethora of autocrine, paracrine, and endocrine "bone-forming" factors such as bone morphogenetic proteins [23–25], growth factors [26], prostaglandins [27–31], shared cytokines and chemokines [2], and hormones such as the parathyroid hormone (PTH) [32]. Although all of these molecules appear to be fundamental for the maintenance of bone microarchitecture and stem/progenitor cell homeostatic features within the bone marrow, PTH has been identified as a key niche element that functionally and spatially links the activities of MSCs and HSCs.

PTH Effects Within the Bone Marrow at a Glance

PTH, a peptide comprised of 84 amino acids, is the fundamental regulatory molecule of calcium and phosphate systemic levels; nonetheless, the PTH metabolic features go beyond this and meet the needs of osteocyte signaling, osteoblast proliferation, differentiation and apoptosis, and HSC homing, maintenance, and egression [32, 33].

It is well documented that the administration of PTH, its recombinant human analog PTH 1–34, and its nearly

homologous PTH-related peptide (PTHrP) exerts dose-dependent differential effects in the bone and the bone marrow microenvironment [32].

Intermittent PTH (iPTH) injections in experimental animals induce a progressive and adaptive response in the cell targets enhancing trabecular bone formation with a concomitant minor loss of the cortical bone [34, 35]. iPTH affects the osteoblastic pool by shifting MSC differentiation towards osteoblastogenesis [36] and also increases the number of HSCs probably due to the simultaneous expansion of the osteoblastic cells and, consequently, the fine-tuned interactions between HSCs and osteoblasts [3, 37, 38]. PTH bone marrow anabolic and bone-building effects were observed following defined dose-treatment protocols in rats (80 μg/kg/day for 14 days) [36], mice (40 μg/kg/day for 21 days) [38], and humans (20 μg daily for 24 months) [39]. Nonetheless, hematopoietic progenitors are preferentially sustained by the early-osteoblastic lineage and PTH administration boosts this anabolic scenery [40]. Certainly, iPTH administration has opened up new avenues for the treatment of bone diseases such as osteoporosis and immune disorders, and iPTH administration could be of use in the future to affect bone marrow transplantation/engraftment outcomes.

In contrast to the anabolic effects of intermittent PTH administration, chronically elevated PTH levels have catabolic effects. Such supraphysiological PTH levels occur in pathological conditions such as primary and secondary hyperparathyroidism, chronic renal disease, and chronic inflammation, all of which induce osteopenia. Actually, modern concepts have portrayed osteopenia and osteoporosis as an "accident of inflammation" [41]. In this context, PTH levels are increased within an acute inflammatory scenario and continuous PTH production drives bone resorption and loss of both the cortical and trabecular bones. Moreover, in the context of inflammation, activated immune cells can release PTHrP, which has been shown to be overexpressed in both acute and chronic inflammation [42, 43]. Continuous PTH administration and/or release within the bone marrow leads to abnormal production of factors that affect hematopoietic lineage commitment. For instance, cPTH enhances receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (MCSF) release by osteoblasts and consequently prompts osteoclast differentiation and activation and diverting the fate of HSCs toward the maturation of myeloid progenies. On the other hand, it has been observed that MSCs and osteoblasts release less osteoprotegerin (OPG) (a decoy receptor of RANKL) after cPTH injection [44, 45]. Nevertheless, treatment with PTH at high doses (13.6 μg/kg/day) for 18–24 months was found to increase the risk of osteosarcoma in rats due to the exaggerated bone formation response provided by the PTH receptors on the osteoblastic cells [46].

The Role of PTH in HSC Niche Regulation

PTH Influences HSCs via Specific MSC Subpopulations and Release of Cytokines and Chemokines

Several studies support the thesis that proper functioning of the bone marrow niche is based on complex interactions between ligands and receptors, as well as physical interactions between the different bone marrow niche residents. In this perspective, PTH provides signals for stem cell differentiation, proliferation, and maintenance, via its specific receptors (PTHR) expressed by the osteoblastic lineage as well as by MSCs within the marrow. An important note is that these receptors are not present in HSCs: this observation indicates that mesenchymal populations and, as recently reported, T-lymphocytes are solely responsible for mediating the effects of PTH within the marrow niche [37, 47–49]. The PTH niche targets are summarized in Fig. 1.

PTH osteogenic activity and its capacity to stimulate MSC expansion have been correlated with HSC homing and the increase of the HSC pool. PTH orchestrates an operational platform among osteoblasts, MSCs, and HSCs, recruiting mediators capable of "sewing the niche patchwork," such as N-cadherin, Wnt/β-catenin, and Notch/Jagged1 [33, 37]. In point of fact, PTH stimulates hematopoiesis in mice via up-regulation of cadherin-11 expression in MSCs. Of interest, cadherin-11 is also highly expressed in hematopoietic progenitors characterized by elevated self-renewal capacity [50, 51]. PTH-induced cadherin-11 production in MSCs can facilitate physical interactions between hematopoietic progenitors and MSCs and, as a consequence, hematopoietic progenitor cell expansion. PTH treatment in mice subjected to lethal irradiation and bone marrow transplantation led to increased cadherin-11 levels in MSCs with concomitant HSCs expansion, substantially improving the survival rate of the experimental animals [52]. Bearing in mind that cadherin-11 interacts with β-catenin [53] and that Wnt/β-catenin activation in hematopoietic progenitor cells contributes to their expansion [54], the above findings depict an effective operating system through bone and immune progenitor cells within the niche.

Exogenous PTH increases the bone marrow cell secretion of important niche regulators such as interleukin (IL)-6, IL-11, GM-CSF, and SCF. In a synergistic fashion, these cytokines enhance the number and mobilization of HSCs [55]. A possible explanation for PTH-induced HSC expansion is based on SCF^+-secreting cell growth and cytokine release; SCF^+-secreting cells in combination with IL-6 and IL-11 secreted inside the niche frames act as signal platform for HSC expansion. In point of fact, SCF expressed by osteoblasts, fibroblasts, *CXCL12*-expressing perivascular stromal cells, endothelial cells, and *nestin*-expressing MSCs has been identified as a critical mediator of HSC dynamics [15]. Furthermore, considering the fact that IL-6 is a downstream mediator of

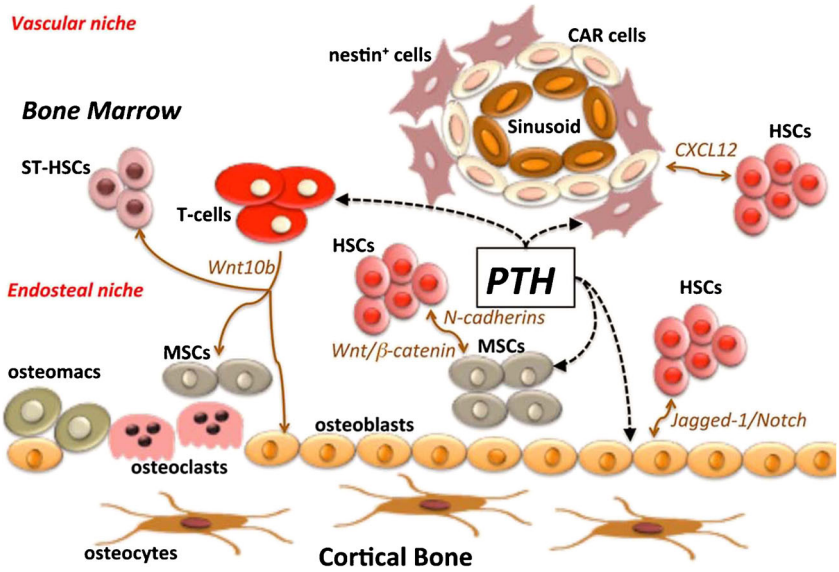

Fig. 1 PTH targets distinct bone marrow elements within an anabolic scenario. Notably, intermittent administration of PTH affects early osteoblastic cells, MSCs, and T cells, inducing multiple spatiotemporal effects. Due to its many effects and its involvement in MSC and HSC homeostasis, PTH has been identified as one of the major regulators for the maintenance of the bone marrow phenotype. The *dashed lines* represent PTH target cells. HSCs hematopoietic stem cells; MSCs bone marrow mesenchymal/stromal stem cells

PTH signaling [56], this cytokine can also directly support PTH-mediated HSC expansion and coordinate hematopoiesis, lymphopoiesis, and megakaryopoiesis [57, 58]. Of note, the IL-6 soluble receptor sIL-6R has been found upregulated in bone marrow cells after PTH treatment, leading researchers to attribute to this receptor unique orphan homeostatic roles within the niche [59]. Indeed, IL-6 and sIL-6R, in a supportive or independent fashion, enhanced PTH-mediated HSC expansion via a STAT3 signaling cascade. In IL-6 null mice, the action of sIL-6R on hematopoietic cells was sufficient to preserve PTH-mediated HSC expansion and thus guarantee PTH anabolic effects [59].

Among the various players in bone marrow homeostasis, proteoglycan 4 (PRG4) is thought to have a role as a regulator of the HSC niche, due to its involvement in HSC expansion. PRG4 supports basal expression of both niche moderators, CXCL12 and IL-6. PTH induces upregulation of *Prg4* mRNA by osteoblast progenitors within the bone marrow and simultaneous osteoblastic PRG4 secretion, which in turn triggers the release of CXCL12 and IL-6. These events culminate in expansion of HSCs due to PRG4 regulatory and PTH-supporting effects. Though PRG4 has not been considered as a "front row" HSC regulator, the fact that in Prg4−/− mice PTH does not significantly augment the marrow $Lin^{-}Sca1^{+}c\text{-}kit^{+}$ pool reveals the significance of PRG4 in PTH outcomes within the niche [60].

As previously mentioned, $nestin^{+}$ MSCs are spatially associated with HSCs and contribute to HSC maintenance. In line with this observation, PTH administration expands bone marrow $nestin^{+}$ cells and conducts them toward osteoblastic differentiation. In addition, PTH-induced $nestin^{+}$ MSC pool expansion is directly correlated with a parallel expansion of HSCs. Thus, PTH seems to amplify the ability of this peculiar nestin-expressed MSC population to support HSC maintenance within the niche [21], motivating new interest in the structural and functional features of this hormone on the microenvironmental behavior of MSCs and HSCs.

Experiments conducted in humans revealed that long-term teriparatide (PTH 1–34 fragment) administration at FDA-approved doses not only yielded favorable outcomes against post-menopausal osteoporosis, but also increased circulating HSCs in the absence of G-CSF. The dual effects of PTH on bone homeostasis and hematopoiesis seem to follow defined signaling pathways. PTH influences bone growth involving Wnt/β-catenin mechanisms; it also exerts an effect on multiple transductional mediators of MSCs, mature osteoblasts, and osteocytes. Concerning hematopoiesis, PTH outcomes were mostly orchestrated by the early-stage osteoblasts and the activation on their membrane of PTHRs via G-protein (Gsα) signaling cascades. Indeed, mice lacking Gs in cells of the osteoblast lineage present a decrease in pro-B and pre-B cells. Bearing in mind that bone mass may be related to B cell number and, in turn, this process may be regulated by signals downstream of Gs in the osteoblast, it is reasonable to deduce that PTH-PTHR-Gs axis activation may have beneficial effects for immune system maturation [61]. In accordance, teriparatide-activated early osteoblasts within human bone marrow provide a watchdog role in the HSC niche [39].

Of interest, these findings in humans were comparable to results obtained in rodents; in mice treated a short time with PTH, there were increases in circulating HSCs, lymphocytes, and neutrophils, without a reduction in the HSC pool [62]. The effect of PTH on the HSC niche has been studied in mice lacking *Bmi 1* (B lymphoma Mo-MLV insertion 1), an important epigenetic niche regulator. *Bmi 1*-null mice displayed weakened HSC self-renewal and reduced HSC niche elements. Moreover, Bmi 1 maintains MSC populations and drives mesenchymal stem cell differentiation toward

osteoblastic lineage and bone formation via the regulation of alkaline phosphatase, osteocalcin, type I collagen, and Runx2 [63]. Thus, Bmi 1 deficiency affects not only immune cells but also bone stem and progenitor cells, whereas its absence disrupts the niche integrity. In this context, PTH 1–34 administration partially rescued hematopoietic defects in *Bmi 1*-null mice and reestablished the HSC niche microenvironment. Furthermore, PTH partially reversed the premature osteoporosis that occurs in the Bmi 1 knockout mice [64]. These results highlight the many ways PTH maintains niche functionality through MSC and HSC interdependency. Extensive investigation is underway on the action of PTH and its bone marrow cell targets.

PTH Targets T Cells that Prompt ST-HSC Expansion and HSC Commitment

Though MSC subpopulations, early-osteoblastic cells, and osteocytes are thought to be the major targets of PTH, some reports have revealed an unexpected role of T lymphocytes in mediating the osteo-anabolic effects of PTH. In line with these findings, iPTH treatment in mice increased T cell-released Wnt10b, a Wnt ligand that drives osteoblastogenesis by activating Wnt receptors on MSCs and osteoblasts. Strong support for this consideration comes from the finding that iPTH administration prompted a reduction in bone anabolic response in mice with T cell deletion [65, 66]. Furthermore, since Wnt signaling actively participates in hematopoiesis in a dose-dependent manner [67], it has been reported that iPTH treatment in mice modulated T cell Wnt10b production and consequently ST-HSC expansion and ameliorated blood cell engraftment after bone marrow transplantation. Interestingly, iPTH-induced ST-HSC expansion did not compromise the quiescent HSC niche or LT-HSC self-renewal [49]. The fact that iPTH does not increase the number of ST-HSCs at the expense of the LT-HSC pool might break new ground in a therapeutic context, regarding PTH preferential niche targets. Bearing in mind the key role of MSCs and osteoblasts in HSC maintenance and HSC metabolic features, these findings have added another player, T cells, to the scenario of hematopoietic regulation in the bone marrow. On the other hand, it is well known that PTH anabolic protocols establish molecular pathways for bone remodeling and hematopoietic niche maturation via stimulation of bone and blood components. In line with this observation, iPTH induces osteoblast release of monocyte chemoattractant protein-1 (MCP-1), which in turn recruits myeloid precursors and differentiates them into osteoclasts [68]. Nevertheless, it was reported that, after PTH challenge, Th17, a T cell subpopulation, produced IL-17, which participates actively in both bone resorption and control of hematopoietic activities [69].

The Importance of PTH in HSC Bone Marrow Niche Manipulation

Research in bone and bone marrow manipulation has powered the development of heterotopic bone models formed in vivo by transplanted MSCs; these capsular bone-mimicking microenvironments are termed ossicles. PTH treatment plays a key role in bone apposition and HSC engraftment and expansion into these ectopic cortical-like bone assemblies [70]. In mice with PTH-treated ossicles, augmented HSC frequency associated with simultaneous bone growth has been reported. Thus, PTH significantly supports ossicle niche development, probably due to its ability to increase anabolic Jagged-1/Notch signaling through osteoblasts and HSCs, to modulate the HSC niche regulator SDF-1 (referred also as CXCL12) and to increase the number of microvessels within this tissue-engineered scenario. In line with this observation, PTH provides ossicle structural and functional sustenance for hematopoietic long-term multilineage reconstitution cells ($CD150^{+}CD48^{-}CD41^{-}Lineage^{-}$ cells) [38]. A recent study also demonstrated that iPTH administration (40 μg/kg) for 28 days in mice transplanted with human MSC-derived ossicles induced a significant increase in the weight of the humanized ossicles, as compared to untreated littermate controls [71].

An important challenge is the improvement of HSC transplantation techniques and HSC engraftment and egression efficiency. It is well documented that, in patients treated with granulocyte colony-stimulating factor (G-CSF)-based protocols, poor HSC mobilization has been observed. Several authors have noted that targeting the distinct niche populations might improve stem cell-based remedies, since treatments with a combination of cytotoxic drugs influence both osteoblasts and HSCs in experimental animals [36]. In this context, a phase I clinical trial established that PTH exerts a prominent pharmacological role in HSC maintenance during G-CSF-induced mobilization treatment [47]. Generally, G-CSF cotreatment used in allogeneic transplantation techniques provokes a homeostatic imbalance in the regulation of osteoblasts and osteoclasts. Decrease of osteoblast numbers leads to reduced levels of HSPC mobilization regulators such as SDF-1, SCF, and OPN. Moreover, it was found that after short-term G-CSF treatment, osteoblast loss and osteoclast pool expansion altered the fine-tuned signaling between bone remodeling mediators and HSCs [72]. In order to offset bone niche disruption and impaired bone remodeling caused by drug treatment, therapy combining PTH and RANKL to enhance HSC egression was tested. PTH and RANKL countered the side effects of cytotoxic chemotherapy in two ways: first, by triggering the anabolic features of osteoblasts and osteoclasts, and second, by protecting the HSC pool during treatment [36].

Conclusions

Bone marrow homeostasis is related to the specific features of each niche element, and within this complex system, physical interactions and the release of cytokines and hormones govern MSC and HSC homeostasis. PTH plays a leading role in the panorama of interactions inside the bone marrow. Indeed, the administration of an anabolic regimen of PTH supports MSC and osteoblast differentiation and bone deposition, HSC expansion and protection during chemotherapy, HSC post-transplantation engraftment, and ST-HSC pool development and egression. PTH signaling through early osteoblasts and T lymphocytes in the axial and long bones orchestrates hematopoiesis and coordinates niche microenvironmental dynamics. Given the pharmacological potential of PTH and its important physiological role in the niche apparatus, it is to be expected that this key hormone will be the subject of intense future inquiry.

Compliance with Ethical Standards

Conflict of Interest Maria Giovanna Sabbieti, Luigi Marchetti, Roberta Censi, Giovanna Lacava, and Dimitrios Agas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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