Impact of parathyroid hormone on bone marrow-derived stem cell mobilization and migration

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Abstract
Parathyroid hormone (PTH) is well-known as the principal regulator of calcium homeostasis in the human body and controls bone metabolism via actions on the survival and activation of osteoblasts. The intermittent administration of PTH has been shown to stimulate bone production in mice and men and therefore PTH administration has been recently approved for the treatment of osteoporosis. Besides to its physiological role in bone remodelling PTH has been demonstrated to influence and expand the bone marrow stem cell niche as well as to induce mobilization of progenitor cells from the bone marrow into the bloodstream. This novel function of PTH on modulating the activity of the stem cell niche in the bone marrow as well as on mobilization and regeneration of bone marrow-derived progenitor cells offers new therapeutic options in bone marrow and stem cell transplantation as well as in the field of ischemic disorders.

INTRODUCTION
Parathyroid hormone (PTH) is a peptide hormone secreted from the parathyroid glands that mainly acts on bone and kidney cells[1]. PTH is one of the two major hormones modulating calcium and phosphate homeostasis through its action to stimulate renal tubular calcium reabsorption and bone resorption[2]. Human PTH is an 84-amino acid peptide, but the first two amino acids in the N-terminal region of the hormone are mandatory for the activation of the PTH 1 receptor (PTH1r), a membrane surface receptor expressed in multiple tissues including bone and kidney[3]. It has been appreciated that recombinant PTH 1-34 retains all of the biologic activity of the intact peptide (1-84)[4]. Patients with primary or sec-
Prolonged hyperparathyroidism and subsequently chronic exposure to high serum PTH concentrations revealed increased bone resorption[6]. However, in contrast to this observations after chronic exposure to high serum PTH concentrations, the intermittent administration of recombinant PTH in mice and men has been demonstrated to stimulate bone production more than resorption[6]. These observations finally guided the approval of intermittent recombinant PTH (1-34) for the treatment of osteoporosis in postmenopausal woman and subsequently in men[7,8]. Besides to its physiological role in bone remodeling, PTH has been shown to modulate the haematopoietic stem cell (HSC) niche in the bone marrow (BM)[9]. This review will focus on the molecular interplay between PTH and the HSC niche and will also discuss the ability of PTH to mobilize bone marrow-derived stem cells (BMCs) to the peripheral blood, which opens new therapeutic options for PTH in the field of bone marrow and stem cell transplantation as well as a potential role of PTH in the treatment of ischemic disorders.

**PTH AND THE BM STEM CELL NICHE**

BM is a complex organ, consisting of many different haematopoietic and non-haematopoietic cell types, that is surrounded by a shell of vascularized and innervated bone[10]. In the last years, there have been a lot of research and discussions about the existence and localizations of “niches”, specific local tissue microenvironments that maintain and regulate stem cells within the bone marrow[11,12]. The niche hypothesis has been proposed for the first time by Schofield et al[13] in 1978 and since then tremendous progress has been made in elucidating the location and cellular components of the HSC niche. It is now appreciated that the HSC niche is perivascular, created partly by mesenchymal stromal cells and endothelial cells and often, but not always, located near trabecular bone[14-19]. Calvi et al[10] were first able to demonstrate that osteoblastic cells regulate the haematopoietic stem cell niche and that PTH is a pivotal regulator of the HSC microenvironment. They used transgenic mice carrying constitutively activated PTH/PTHrP receptors (PPRs) under control of the osteoblast-specific a1(I) collagen promoter and were able to detect a 2-fold increased number of Lin- Sca-1+ cKit+ (LSK) cells. PPR-stimulated osteoblastic cells produced high levels of the Notch ligand jagged 1 and supported an increase in the number of HSC, as well as the anabolic effect of PTH in bone was confirmed by Weber et al[20]. They showed the ability of PTH to augment Jag-1 expression on osteoblasts in an AC/PKA-dependent manner following 5 consecutive days of PTH administration. Jag-1 protein was increased on specific populations of osteoblasts including those at the endosteum and spindle-shaped cells in the bone marrow cavity[21,22]. PTH stimulation also augments the expression level of N-cadherin on osteoblasts[23,24]. N-cadherin-mediated adhesion may link to the canonical Wnt and Notch1 pathway through b-catenin signaling[25]. Wnt and Notch signaling pathways are known to be important in hematopoietic stem cell renewal[11,26].

As another important regulator of PTH-driven HSC expansion, a number of cytokines have been identified[11]. Several studies demonstrated increased expression of cytokines like IL-6, IL-11, G-CSF and stem cell factor (SCF)[27-30]. In this context, PTH signalling to osteoblasts resulted in an increase in the number of SCF+ cells[31]. Likewise, exposure to PTH resulted in enhanced expression of IL-6 and IL-11 in osteoblasts[32]. Jung et al[33] were able to demonstrate that expression of the chemokine stromal derived factor-1 (SDF-1, also termed CXCL12) and its major receptor CXCR4 are pivotal in mediating both retention and mobilization of HSCs[33] and will be discussed at a later stage in this review. Brunner et al[34] compared a treatment regimen with G-CSF and PTH in a mouse model. They found that in contrast to G-CSF, PTH treatment resulted in an enhanced cell proliferation with a constant level of lin-/Sca-1+/c-kit+ and CD45+/CD34+ subpopulations in bone marrow[35]. Altogether the data on PTH and the bone marrow suggest an important role of PTH on the niche which allows the use PTH as a therapeutic tool to increase the number of BMSC. In the following chapter we will focus on the potential role of PTH to mobilize cells from the bone marrow to the bloodstream.

**PTH AND STEM CELL MOBILIZATION**

Under normal and pathological conditions there is continuous egress of hematopoietic stem and progenitor cells out of the bone marrow to the circulation, termed mobilization[36]. Stem cell mobilization can be achieved experimentally in animal models or clinically by a great variety of agents, such as cytokines (e.g., G-CSF, SCF, Erythropoietin) and small molecules (e.g., AMD3100)[40].

Following the intriguing data of Calvi et al[37] showing that PTH is a pivotal regulator of the HSC microenvironment and is able to increase the number of HSC in contrast, animals receiving pulse dosing of PTH had improved outcomes with 100% survival. The bone marrow histology of the two groups was also substantially different, with an increase in cellularity and a decrease in fat cells in the PTH-treated group[38]. That Jagged1 may play a critical role in mediating the PTH-dependent expansion of HSC, as well as the anabolic effect of PTH in bone was confirmed by Weber et al[20]. They showed the ability of PTH to augment Jag-1 expression on osteoblasts in an AC/PKA-dependent manner following 5 consecutive days of PTH administration. Jag-1 protein was increased on specific populations of osteoblasts including those at the endosteum and spindle-shaped cells in the bone marrow cavity[21,22]. PTH stimulation also augments the expression level of N-cadherin on osteoblasts[23,24]. N-cadherin-mediated adhesion may link to the canonical Wnt and Notch1 pathway through b-catenin signaling[25]. Wnt and Notch signaling pathways are known to be important in hematopoietic stem cell renewal[11,26].

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the BM, several preclinical studies investigated the effect of PTH administration on stem cell mobilization in mice. Adams et al. used three mouse models that are relevant to clinical uses of HSCs to test the hypothesis that targeting the niche might improve stem cell-based therapies. They treated mice with PTH for 5 wk following a 5-d regimen of G-CSF to mobilize BMCs from the bone marrow to the peripheral blood. They demonstrated that PTH administration increased the number of HSCs mobilized into the peripheral blood for stem cell harvests, protected stem cells from repeated exposure to cytotoxic chemotherapy and expanded stem cells in transplant recipients. These results were corroborated by a study of our group where we explored the potency of PTH compared to granulocyte colony-stimulating factor (G-CSF) for mobilization of stem cells and its regenerative capacity on bone marrow. Healthy mice were either treated with PTH, G-CSF, or saline. HSCs characterized by lin-/Sca-1+/c-kit+ were subpopulations (CD31+, c-kit+, Sca-1+, CXCR4+) of CD45+/CD334+ and CD45+/CD34- cells were measured by flow cytometry. Immunohistology as well as fluorescent-activated cell sorting analyses were utilized to determine the composition and cell-cycle status of bone marrow cells. Serum levels of distinct cytokines [G-CSF, vascular endothelial growth factor (VEGF)] were determined by enzyme-linked immunosorbent assay. Stimulation with PTH showed a significant increase of all characterized subpopulations of bone marrow-derived progenitor cells (BMDCs) in peripheral blood (1.5- to 9.8-fold) similar to G-CSF. In contrast to G-CSF, PTH treatment resulted in an enhanced cell proliferation with a constant level of lin-/Sca-1+/c-kit+ and CD45+/CD34+ subpopulations in bone marrow. A combination of PTH and G-CSF showed only slight additional effects compared to PTH or G-CSF alone. Interestingly, treatment with PTH resulted in significantly elevated concentrations of G-CSF in serum suggesting an indirect mobilizing effect of PTH via stimulation of osteoblasts producing G-CSF. To verify this hypothesis, PTH-stimulated mice were pre-treated with a G-CSF antibody and, thereby, the mobilizing effect could be significantly inhibited. In a more clinically relevant model Brunner et al. investigated prospectively the effect of primary hyperparathyroidism (PHPT), a condition with high PTH serum levels, on mobilization of BMDCs in humans. In 22 patients with PHPT and 10 controls defined subpopulations of circulating BMDCs were analyzed by flow cytometry. They found a significant increase of circulating BMDCs and an upregulation of SDF-1 and VEGF serum levels in patients with PHPT. The number of these circulating cells positively correlated with PTH serum levels. Interestingly, the number of circulating BMDCs returned to control levels measured after surgery.

Because of the therapeutic potential of PTH to activate and increase the number of HSCs in preclinical models, a phase I trial in humans has been conducted. A group of 20 human patients were included who had previously failed to produce a sufficient number of CD34+ HSCs in their peripheral blood following mobilization. Subjects were treated with PTH in escalating doses of 40 µg, 60 µg, 80 µg, and 100 µg for 14 d. On days 10-14 of treatment, subjects received filgrastim (G-CSF) 10 µg/kg. PTH administration was tolerated well and there was no dose-limiting toxicity. Of those patients who previously had a single mobilization failure, 47% met therapeutic mobilization criteria, of those who had previously failed two attempts at mobilization, the post PTH success rate was similar (40%).

**PTH AND STEM CELL HOMING VIA SDF1/CXCR4**

In light of the promising results showing increased mobilization of BMDCs after treatment with PTH, several studies also focused on the migration of different BMDCs after PTH pulsing. The main axis of stem cell migration and homing is the interaction between SDF-1α and the homing receptor CXCR-4, which is expressed on many circulating progenitor cells. It has been shown that CXCR-4- and SDF-1α-deficient mice have a severe migration defect of HSCs from the embryonic liver to the bone marrow by the end of the second trimester. At this period of development, SDF-1 is upregulated in bone marrow and chemoattracts HSCs. Later in life the SDF-1-CXCR4 axis plays a crucial role in the retention and homing of HSCs in the bone marrow stem cell niche. SDF-1 is expressed by different cell types, including stromal and endothelial cells, bone marrow, heart, skeletal muscle, liver and brain. Active SDF-1 binds to its receptor CXCR-4 and is cleaved at its position 2 by CD26/dipeptidylpeptidase IV (DPP-IV), a membrane-bound extracellular peptidase. The truncated form of SDF-1 not only loses its chemotactic properties, but also blocks chemotaxis of full length SDF-1. DPP-IV is expressed on many hematopoietic cell populations and is present in a catalytically active soluble form in the plasma. In a chimeric mouse model to track BMDCs by ubiquitously expressing EGFP under control of the ubiquitin C promoter, Brunner et al. demonstrated reduced migration of CXCR-4+ BMDCs associated with decreased expression levels of the corresponding growth factor SDF-1 in ischemic myocardium after treatment with G-CSF. This could be explained by N-terminal cleavage of CXCR4 on mobilized haematopoietic progenitor cells resulting in loss of chemotaxis in response to SDF-1. In contrast, PTH treated animals revealed an enhanced homing of BMDCs associated with an increased protein level of SDF-1 in the ischemic heart. Jung et al. showed recently enhanced levels of SDF-1 in the bone marrow after PTH stimulation. Therefore, our group used an enzymatic activity assay to investigate whether the elevated levels of SDF-1 protein in the ischemic heart after PTH stimulation may be due to changes of DPP-IV activity. Indeed, we were able to demonstrate that PTH inhibited the activity of
There is a long-lasting interest in the cardiovascular effects of PTH. It has been shown that cardiovascular cells, cardiomyocytes and smooth muscle cells are target cells for PTH. PTH is known to induce arterial vasodilation, which is based on the activation of PTH/PTHrP receptor type 1. Upon receptor activation, PTH causes an increase of cAMP production leading to a decreased calcium influx resulting in vasodilation.

After Calvi et al. established that PTH could alter the HSC niche resulting in HSC expansion and the fact that PTH treatment improved dramatically the survival of mice receiving bone marrow transplants, there was an emerging interest on a potential cardioprotective role of PTH. First, Zaruba et al. exploited the impact of PTH on post-MI survival and functional parameters in a murine model of myocardial infarction. They injected the biological active fragment of PTH [PTH1-34] for up to 14 consecutive days. PTH treatment after MI exerted beneficial effects on survival and myocardial function 6 and 30 d after MI which was associated with a smaller infarct size. Furthermore, PTH treated animals revealed an augmented mobilization and homing of angioenic CD45+/CD34+ BMCs associated with an improved neovascularization. In a more recent study, the effect of G-CSF, PTH, and the combination of both was investigated using the innovative pinhole single photon emission computed tomography (SPECT) technique, which allows non-invasive, repetitive, quantitative, and especially intra-individual evaluations of infarct size. SPECT analyses revealed that PTH treatment resulted in a significant reduction of perfusion defects from day 6 to day 30 in contrast to G-CSF alone. A combination of both cytokines had no additional effects on myocardial perfusion. To further elucidate the cardioprotective mechanism of PTH, our group focused on the pivotal SDF-1/CXCR4 axis. PTH treatment again significantly improved myocardial perfusion defects from day 6 to day 30 in contrast to G-CSF alone. A combination of both cytokines had no additional effects on myocardial perfusion. To further elucidate the cardioprotective mechanism of PTH, our group focused on the pivotal SDF-1/CXCR4 axis. PTH treatment again significantly improved myocardial function after MI associated with enhanced homing of CXCR4+ BMCs to the ischemic myocardium. Interesteedly, stem cell homing and functional recovery were both reversed by blocking the SDF-1/CXCR4 axis using the CXCR4 antagonist AMD3100. PTH injections in transgenic G-CSF deficient mice showed that the cardioprotective effects of PTH are independent of endogenous G-CSF release.

That PTH treatment not only exerts beneficial effects in ischemic cardiovascular disorders shows a recent work where PTH therapy was tested after ischemic stroke in mice. PTH treatment significantly increased the expression of cytokines including VEGF, SDF-1, BDNF and Tie-1 in the brain peri-infarct region. Moreover, PTH treatment increased angiogenesis in ischemic brain, promoted neuroblast migration from the subventricular zone and increased the number of newly formed neurons in the peri-infarct cortex. Furthermore, PTH-treated mice revealed better sensorimotor functional recovery compared to vehicle-treated mice.

**Figure 1** Impact of parathyroid hormone on mobilization and homing of bone marrow-derived stem cells. Left axis: PTH administration results in mobilization of BMCs from bone marrow into peripheral blood via endogenous release of G-CSF. Right axis: PTH results in down-regulation of DPPIV, which inhibits inactivation of SDF-1 and therefore promotes homing of CXCR4+ BMCs. PTH: Parathyroid hormone; BMCs: Bone marrow-derived stem cells; G-CSF: Granulocyte colony-stimulating factor; SDF-1: Stromal cell-derived factor-1.

**DPP-IV in vitro and in vivo**. In order to exploit whether the observed enhanced stem cell homing after PTH treatment was dependent on an intact SDF-1/CXCR4 axis, the CXCR4 antagonist AMD3100 was injected along with PTH. In fact, the number of CD34+/CD45+ BMCs was significantly decreased in mice treated with PTH and AMD3100 compared to animals treated solely with PTH. A similar pharmacological concept has been done recently by Zaruba et al. They used a dual non-invasive therapy based on mobilization of stem cells with G-CSF and pharmacological inhibition of the protease DPP-IV/CXCR4 axis. PTH administration results in mobilization of BMCs from bone marrow into peripheral blood via endogenous release of G-CSF. Right axis: PTH results in down-regulation of DPPIV, which inhibits inactivation of SDF-1 and therefore promotes homing of CXCR4+ BMCs. PTH: Parathyroid hormone; BMCs: Bone marrow-derived stem cells; G-CSF: Granulocyte colony-stimulating factor; SDF-1: Stromal cell-derived factor-1.

In summary, data on preclinical and clinical studies reveal that PTH is a promising substance to enhance migration and homing of BMCs to ischemic tissue due to modulation of the pivotal SDF-1/CXCR4 axis.

**PTH FOR THE TREATMENT OF ISCHEMIC DISORDERS**

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pared to stroke controls.[8]

CONCLUSION

In summary, experimental and clinical data suggest a novel function of PTH on modulating the activity of the bone marrow stem cell niche as well as on mobilization and homing of BMCs. PTH is a natural DPP-IV inhibitor and is able to increase SDF-1 protein level in ischemic tissue, which enhances recruitment of regenerative BMCs associated with improved functional recovery. Based on the fact that PTH has already been clinically approved in patients with osteoporosis,[9] the data offer new therapeutic options for PTH in bone marrow and stem cells transplantation as well as in the field of ischemic disorders (Figure 1).

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