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Parathyroid Hormone (PTH) and Hematopoiesis: New Support for Some Old Observations

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Abstract Forty-seven years ago, the parathyroid hormone (PTH) in one injection of Lilly's old bovine parathyroid extract, PTE, was found to greatly increase the 30-day survival of heavily X-irradiated rats when given from 18 h before to as long as 3 h after irradiation but no later. This was the first indication that PTH might stimulate hematopoiesis. Recent studies have confirmed the relation between PTH and hematopoiesis by showing that hPTH-(1-34)OH increases the size of the hematopoietic stem cell pool in mice. The peptide operates through a cyclic AMP-mediated burst of Jagged 1 production in osteoblastic cells lining the stem cells' niches on trabecular bone surfaces. The osteoblastic cells' Jagged 1 increases the hematopoietic stem cell pool by activating Notch receptors on attached stem cells. PTH-triggered cyclic AMP signals also directly stimulate the proliferation of the hematopoietic stem cells. However, the single PTH injection in the early experiments using PTE probably increased the survival of irradiated rats mainly by preventing the damaged hematopoietic progenitors from irreversibly initiating self-destructive apoptogenesis during the first 5 h after irradiation. It has also been shown that several daily injections of hPTH-(1-34)OH enable lethally irradiated mice to survive by stimulating the growth of transplanted normal bone marrow cells. If the osteogenic PTHs currently entering or on the verge of entering the market for treating osteoporosis can also drive hematopoiesis in humans as well as rodents, they could be potent tools for reducing the damage inflicted on bone marrow by cytotoxic cancer chemotherapeutic drugs and ionizing radiation. J. Cell. Biochem. 96: 278–284, 2005.

Key words: adenylyl cyclase; apoptosis; β-catenin; bone marrow transplants; CFU-S (colony-forming units-spleen); cyclic AMP; hematopoiesis; HSC (hematopoietic stem cells); Jagged 1; N-cadherin; Notch receptors; PTH (parathyroid hormone); PTHR1 receptor; stem cell niche; trabecular bone-lining cells; Wnt; X-radiation

The human parathyroid hormone (i.e., r[recombinant] hPTH-(1-84) [Preos^{TM}]) and three of its N-terminal fragments/analogs (rhPTH-(1-34)OH [Forteo^{TM}], rhPTH-(1-31)NH_2 [Ostabolin^{TM}], and [Leu^{27}]*cyclo*(Glu^{22}-Lys^{26}) hPTH-(1-31)NH_2 [Ostabin-C^{TM}]) have become clinically very important because of their abilities to strongly stimulate bone formation and consequently treat osteoporosis, to accelerate fracture healing and to accelerate and strengthen implant anchorage [reviewed by Whitfield, 2005a,b,c]. But they can do more than stimulate bone growth because the PTHR1 (or PTH1R) receptors that they activate are widely expressed by the cells of many tissues where they are meant to be activated by autocrine and paracrine PTHrP (or more specifically PTHrP's N-terminal region) to drive various differentiation programs [reviewed by Whitfield, 2005a]. For example they can also modulate vascular ossification and reduce psoriatic lesions [Whitfield, 2004, 2005a,b,c].

There is a large body of evidence obtained between 1958 and 1974 and more recently in 2003 for parathyroid hormone (PTH) also stimulating hematopoiesis in mice and rats. This suggests that the PTHs might eventually be used to enhance the ability of bone marrow transplants or endogenous marrow progenitor cells to restore cancer patients' bone marrow depleted by radiation or cytotoxic chemotherapeutic drugs and to treat victims of reactor accidents.

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OLD EVIDENCE

The story of PTH and hematopoiesis began in 1958 in the pages of Nature where R.H. Rixon, J.F. Whitfield, and T. Youdale reported the surprising ability of Eli Lilly's PTE (bovine parathyroid extract) to significantly increase the survival of X-irradiated rats. This was the same PTE that H. Selye had used 36 years earlier to demonstrate another unexpected ability of PTH; the dramatic stimulation of osteogenesis in rat pups [Selye, 1932]. Three years later, Rixon and Whitfield [1961], reported the results of a further 59 experiments using 1,296, 300-g males of a laboratory strain of hooded rats. They found that just one maximally effective dorsothoracic subcutaneous injection of PTE containing 50–200 USP units of PTH activity between 18 h before and 3 h after irradiation with 7.0–8.5 Gy (700–850 rads) of 2 MeV X-rays significantly increased the number of animals that survived for 30 days after irradiation. For example, 33% of untreated rats irradiated with 8.0 Gy were living 30 days later while 73% of rats that had received PTE with 200 USP PTH units 5 min after irradiation were alive and well by 30 days ($P < 0.001$). But by 5 h after irradiation an injection of PTE with 200 U of PTH activity could no longer increase the 30-day survival.

Since the fraction of hematopoietic stem and precursor cells surviving irradiation with X-ray doses between 7.0 and 8.5 Gy, would have determined how many rats were living 30 days later, the considerable therapeutic effectiveness of PTE suggested that it had somehow stimulated enough of these cells to repopulate depleted bone marrows and enable more rats to survive. But Rixon et al. had the same problem as Selye in 1932. Was it the PTH or something else in the Lilly extract that stimulated rat bone growth in 1932 and was it the PTH activity that saved irradiated rats in 1958 and 1961?

Unfortunately, there was no pure bovine PTH in the early 1960s with which to answer this question. The currently popular hPTH-(1-34)OH (Lilly's Forteo^{TM}) did not appear until the early 1970s and then not commercially [Potts et al., 1971; Tregear et al., 1974]. So it was necessary to use the animals' own endogenous PTH. This was done by lowering the circulating free (ionic) Ca^{2+} concentration by injecting the Ca^{2+}-chelating EDTA or the Ca^{2+}-binding Na-caseinate, either of which would trigger the release of PTH from parathyroid chief cells by silencing the cells' secretion-suppressing CASRs (Ca^{2+}-sensing receptors) [Mithal and Brown, 2003] (Fig. 1). Nowadays, endogenous PTH release would be triggered with a CASR-silencing "calcilytic" [Nemeth et al., 2001].

In 1966 Perris and Whitfield [1966] reported that injecting 125-g male Sprague–Dawley rats intraperitoneally with EDTA almost halved the circulating free Ca^{2+} concentration within 10 min and significantly stimulated total femoral bone marrow cell proliferation. Then Rixon and Whitfield [1969] showed that one intraperitoneal injection of enough Na-caseinate to halve the circulating free Ca^{2+} concentration in female CF_1 mice doubled the proliferation of femoral bone marrow cells and tripled the pro-

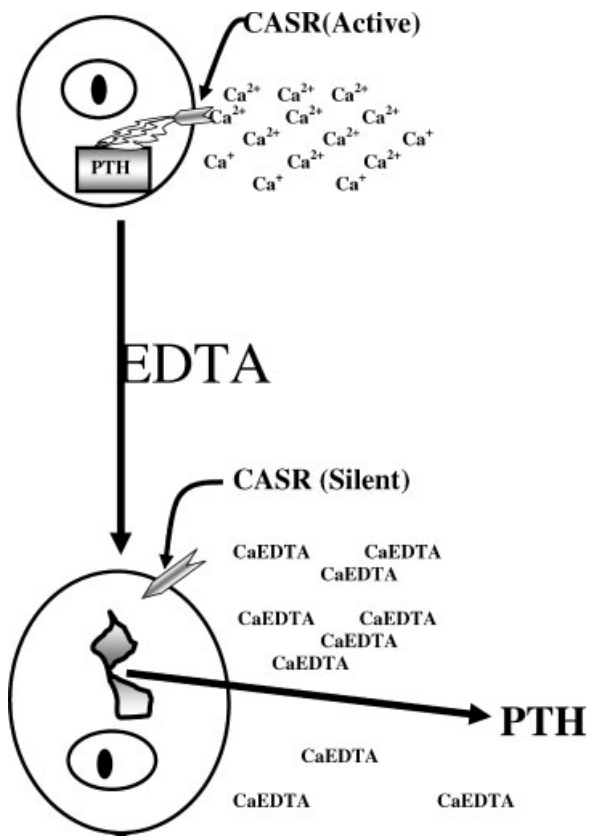

Fig. 1. The release of endogenous PTH from parathyroid chief cells by the Ca^{2+}-chelating EDTA. The release of endogenous PTH from the parathyroid chief cells is controlled by the cells' CASRs (Ca^{2+}-sensing receptors) [Nemeth et al., 2001; Mithal and Brown, 2003]. If there is sufficient circulating Ca^{2+} the CASR signaling restrains the release of PTH, but if the receptors are directly silenced by a ''calcilytic'' inhibitor [Nemeth et al., 2001] or by reducing the circulating free Ca^{2+} concentration with a chelator such as EDTA, the CASR signaling is reduced and the restraints on parathyroid release are lifted.

liferative activity in the femoral bone marrows of mice irradiated with 6.0 Gy (600 rads) of 300 KVp x-rays. Moreover the Na-caseinaate injection increased the 30-day survival of the irradiated mice from 45% to 80%. Na-caseinate also stimulated femoral bone marrow cell proliferation in normal but not TPTXed (thyroparathyroidectomized) male Sprague–Dawley rats, which indicated the mediation of the proliferative response by endogenous PTH [Rixon and Whitfield, 1969].

Then, Rixon and Whitfield [1972] showed that removing either the parathyroid glands (PTX) or the whole thyroid-parathyroid complex (TPTX) from male Sprague–Dawley rats caused a large drop in the mitotic activity in the femoral bone marrow. This drop was followed within 8 days after the parathyroid removal by a 40% drop in the size of the marrow's total nucleated cell population which was largely due to an enormous (ca. 70%) reduction of the erythroid and lymphoid subpopulations. As expected, the dramatic erythroid hypoplasia in the bone marrows of HPX and TPTX rats was accompanied by a 68% drop in the reticulocyte fraction of the non-nucleated marrow cell population, an equally profound depression of ^{59}Fe incorporation into peripheral erythrocytes and a slowing of the recovery of the hematocrit from the normal 5 to 9 days after hemorrhage [Perris and Whitfield, 1971; Perris et al., 1971]. Erythropoiesis in these parathyroidless rats and the post-hemorrhage rate of hematocrit restoration were normalized by daily subcutaneous injections of purified bovine PTH purchased from the now defunct Wilson Laboratories in Chicago. It should also be added in passing that PTX was also found to reduce, and the purified PTH to restore, the primary immune response of rats to injection of sheep erythrocytes [Swierenga et al., 1976]. Thus, by this time it was clear that it was the PTH activity in the Lilly PTE that had saved Rixon et al.'s heavily X-irradiated rats and that PTH somehow controls hematopoiesis in mice and rats. But did the hormone act directly on hematopoietic progenitors or indirectly by controlling the blood Ca^{2+} concentration?

In 1974, Gallien-Lartigue and Carrez reported the results of experiments that showed that PTH can directly target mouse hematopoietic stem cells. They showed this using Till and McCulloch [1961]'s spleen colony assay in which mouse femoral bone marrow cells are suspended in a suitable medium (e.g., Fischer's medium), an appropriate number of cells are then injected into lethally irradiated mice, and the numbers of colonies formed in the animals' spleens by hematopoietic stem cells and early-stage precursor cells (HSC [hematopoietic stem cells] per CFU-S [colony-forming unit-spleen] cells) in the injected marrow suspension are counted around 10 days later [Keller, 1992]. Gallien-Lartigue and Carrez specifically used the "thymidine suicide" technique [Becker et al., 1965; Byron, 1977; Schofield, 1979] to find out whether pure bovine PTH from Calbiochem could directly stimulate CFU-S cell proliferation. In this technique, femoral bone marrow cells are suspended in medium and incubated for 2.5 h and then incubated for a further 30 min in medium containing a relatively high radioactivity (e.g., 200 μCi [7.4 MBq]/ml) from high-specific activity ^{3}H-thymidine. If the CFU-S cells are already making DNA when suspended or are stimulated to do so after suspension, they will incorporate ^{3}H-thymidine from the medium into their DNA and be killed by the chromosome damage inflicted by the β-particles emitted by the ^{3}H. And Gallien-Lartigue and Carrez [1974] found that the PTH did stimulate CFU-S cells to suicidally start replicating DNA as indicated by reduction of spleen colony formation when the PTH-treated marrow cell suspensions were injected into lethally irradiated mice. The hormone specifically stimulated the prompt initiation of DNA replication by a population of CFU-S cells that were paused in a late G_1 (i.e., prereplicative) state [Gallien-Lartigue and Carrez, 1974].

Since injecting CFU-S cells was (and still is) known to save lethally irradiated mice [Schofield, 1979; Nakorn et al., 2002], stimulating the proliferation of surviving CFU-S cells could have been how the PTH activity in the Lilly PTE saved Rixon et al. [1958], Rixon and Whitfield [1961] irradiated rats. But the story of PTH and hematopoiesis stopped at this point and languished in electronically inaccessible archives for 30 years. But PTH's ability to stimulate hematopoiesis has been recently rediscoverd.

PTH AND HEMATOPOIESIS: REDISCOVERY AND EMERGING MECHANISMS

It has been known since the 1970s that HSC/CFU-S cells are somehow associated mainly

with bone cells [Lord et al., 1975; Schofield, 1978, 1979; Mason et al., 1989; Lord, 1990; Nilsson et al., 2001]. It has now been shown that mouse HSC cells (specifically "long-term" HSC cell) are tethered to N-cadherin-expressing, spindle-shaped osteoblastic cells lining trabecular bone [Zhang et al., 2003; Zhu and Emerson, 2004] (Fig. 2). Consequently increasing trabecular bone surfaces increases the number of niches and HSC cells to fill them [Zhang et al., 2003; Zhu and Emerson, 2004]. The HSC cells are tethered tightly to the trabecular bone-lining cells by N-cadherin mooring lines connected to the HSCs' Wnt/Frizzled receptor/β-catenin mechanism signals from which maintain the HSC/CFU-S pool by promoting HSC self-renewal rather than terminal differentiation [Reya et al., 2003; Willert et al., 2003; Staal and Clevers, 2005] (Fig. 2). But there is another player in this complex HSC-driving mechanism—Notch (Fig. 2). Besides enabling the accumulation of nucleus-seeking, gene-activating β-catenin, signals from the Wnt receptor-driven mechanism might also enable the accumulation of the Notch receptor's nucleus-seeking, gene-activating cytoplasmic fragment which would also be needed to maintain the HSC cells' self-renewing, niche-bound "stemness" [Duncan et al., 2005].

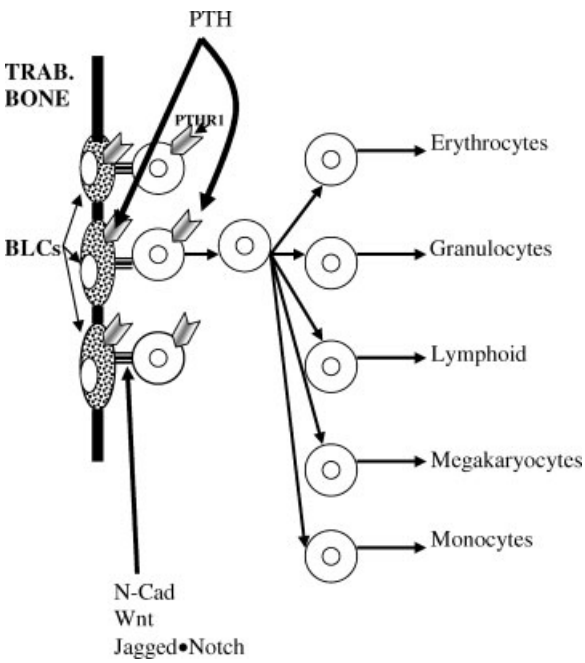

Fig. 2. The control of HSC proliferation and differentiation by adenylyl cyclase-activating PTHR1 receptors. The HSC cells' niches are on trabecular bone (TRAB.BONE) surfaces. The stem cells are tethered to the bone-lining cells (BLCs) by N-cadherin links which together with a signaling complex consisting of the Wnt/Wnt receptor (Frizzled)/β-catenin and Jagged1/Notch mechanisms keep the HSS/CFU-S cells in the self-renewing stem cell state instead of terminally differentiating. Cyclic AMP signals from PTH-activated PTHR1 receptors enlarge HSC/CFU-S pool by: (1) increasing the amount of trabecular bone and with it the available niche space; (2) stimulating the lining cells to make large amounts of Jagged1 which activates the Notch receptors on the attached HSC/CFU-S cells; and (3) directly stimulating the HSC/CFU-S cells to start replicating DNA. Without endogenous PTH the HSC/CFU-S pool shrinks as the cells terminally differentiate and hematopoiesis declines.

The osteogenic PTHs could increase the marrow HSC/CFU-S pool size, and with this hematopoietic potency, in at least four ways. First they strongly stimulate the growth of trabecular bone [Whitfield, 2005a], which could enlarge the HSC/CFU-S niche space [Zhang et al., 2003]. Second, they would promote the attachment of HSC cells to the expanding niches by stimulating the expression of N-cadherin mooring lines by the osteoblastic niche-lining cells [Suva et al., 1994; Marie, 2002]. Third, they could directly stimulate CFU-S cells [Gallien-Lartigue and Carrez, 1974]. And fourth, Calvi et al. [2003] have shown that the adenylyl cyclase-stimulating hPTH-(1-34)OH, the potent adenylyl cyclase-stimulating forskolin, or a permanently switched-on mutant PTHR1 receptor (which does not need a PTH to activate it) can enlarge a mouse's HSC pool by causing the bone-lining cells to make large amounts of Jagged 1 which activates Notch receptors on the linked HSC cells. It should be noted parenthetically that the ability of other adenylyl cyclase stimulators such as the β-adrenergic agonist isoproterenol and dibutyryl-cyclic AMP to stimulate mitotic activity in rat bone marrow and murine CFU-S cells was established between 1970 and 1977 by Byron [e.g., Byron, 1977] and Rixon et al. [1970]. It follows from this that eliminating endogenous PTH by HPX or TPTX should lift the restraints on HSC differentiation which would shrink the stem cell pool and cause the dramatic decline of hematopoiesis observed by Perris and Whitfield [1971], Perris et al. [1971], and Rixon and Whitfield [1972].

SUMMARY AND FUTURE PROSPECTS

We can now update the story of Lilly's PTE and the survival of Rixon et al's heavily X-irradiated rats. It was indeed the PTH activity in the extract that more than doubled the rats'

30-day survival. But it was unlikely that the PTH would have saved animals injected as long as 3 h after irradiation by expanding marrow HSC/CFU-S pools although pool expansion might have contributed to the survival of the rats injected 18 h before irradiation. Since a large fraction of such heavily irradiated bone marrow hematopoietic cells would have killed themselves by initiating apoptosis during the first few hours after irradiation [Whitfield et al., 1965; Peng et al., 1998, 1999; Drouet et al., 1999; Goud, 1999; Vavrova et al., 2002; Bertho et al., 2004], PTH had little time to stop them from doing so when it was injected after irradiation. Therefore, another of PTH's many actions, triggering the anti-apoptotic action of cyclic AMP-dependent protein kinase activity [Findik et al., 1995; Garcia-Bermejo et al., 1998; Li et al., 2000; Virdee et al., 2000; Bellido et al., 2001; Chae et al., 2001; Plotkin et al., 2002; Sowa et al., 2003; Chen et al., 2004; Hastings et al., 2004; Martin et al., 2005], was probably the main reason for the increased 30-day survival of rats when PTE was injected between 5 min and 3 h after irradiation. However, by 5 h after irradiation it would have been too late for PTH do anything for the salvageable HSC/CFU-S cells—they would have been apoptotic or irreversibly on the road to apoptosis [Whitfield et al., 1965; Peng et al., 1998, 1999; Drouet et al., 1999; Goud, 1999; Vavrova et al., 2002; Bertho et al., 2004].

In conclusion, the osteogenic PTH's on the market or coming there soon could be valuable tools for treating the hematopoietic damage inflicted on cancer patients by radiation and cytotoxic chemotherapeutic drugs and victims of reactor accidents. Another more recent foretaste of what they might do for such patients has been provided by Calvi et al. [2003]. They lethally irradiated mice and then injected just enough marrow cells from normal donor animals to allow 27% of the irradiated animals to survive by 28 days. But when the irradiated animals also received intermittent injections of hPTH-(1-34)OH (Forteo^{TM}), 100% of them survived with increased loads of transplanted marrow cells in their hind limbs.

The abilities of the available osteogenic PTHs to stimulate rodents' endogenous and transplanted HSC pools should now be compared. But of course it is most important to find out whether the PTHs can stimulate human as well as rodent hematopoiectic stem cells.

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