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REVIEW

Osteoclasts and hematopoiesis

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The skeletal tissue is closely associated with the hematopoietic tissue lodged in its inner cavities. Besides the well-known role of the endosteal osteoblasts in the maintenance of the hematopoietic stem cell (HSC) niche, it is an emerging concept that osteoclasts are involved in the regulation of hematopoiesis as well, although published data are still incomplete and somehow controversial. We reviewed the literature, and report here our perspective on the close relationship between bone resorption and HSC permanence in bone or egress to the circulation. We discussed the pressure that bone diseases exert on the development of hematological alterations, as well as the role of calcium and osteoclast enzymes in the regulation of HSC homeostasis. Genetic studies and preclinical experiments are described, which unveiled how bone disorders and treatments aimed at restoring the bone mass affect hematopoiesis, with consequent clinical implications. We conclude that this new field of investigation must be extended to unequivocally establish the role of osteoclasts in myelopoiesis and lymphopoiesis, and to envision treatments that can help hematological failures to be cured along with the associated bone alterations.

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Introduction

The skeleton is characterized not only by a shell of mineralized tissue but also by inner cavities lodging the bone marrow that supplies all peripheral blood elements.[1] Osteoblasts are well-known niche components that are indispensable for keeping hematopoiesis lifelong,[2] and do so through their interactions with hematopoietic stem cells (HSCs).[3] The true nature of the osteoblastic HSC niche is, however, still controversial. According to recent reports,[4] mature osteoblasts are unlikely to support HSCs because the ablation of osteocalcin-positive cells, assumed to be at a late stage of maturation into the osteoblast lineage, does not influence hematopoiesis.[5] Likewise, strontium ranelate, which increases the number of mature osteoblasts, does not increase the number of HSCs in the bone marrow.[6] In contrast, nestin-positive mesenchymal stromal cells interact with HSCs, while PDGFRα/Sca1-positive cells and early osteoprogenitors are able to support hematopoiesis.[7] Furthermore, morphological evidence suggests that pre-osteoblastic cells, which have an aspect similar to fibrotic stromal cells, are better placed to interact with HSCs.[4] In fact, HSCs are not juxtaposed in direct contact with endosteal cells, but are generally enriched within three cell diameters from the endosteal surface, a site where pre-osteoblasts rather than mature osteoblasts are located.

Notwithstanding these hot aspects, many signals and pathways involved in the regulation of HSCs by the osteogenic cells are well known,[2] as are various regulatory molecules derived from the vascular endothelial niche,[7] the innervation,[8,9] the systemic circulation and from various local non-cellular components.[2] Instead, far less known are the interactions between osteoclasts and hematopoiesis, this being a relatively recent field of investigation that is still incomplete and controversial (**Table 1**). We will review what is known so far on this component of the hematopoietic niche, discussing potential regulatory pathways and clinical implications.

Lessons from Osteoporosis and Osteopetrosis

Why should the osteoclast serve as a hematopoietic niche component? The most obvious possibility is with its essential role in creating space into which the hematopoietic tissue expands.[10] There are pathological situations that support this hypothesis, and data mostly arise from clinical and preclinical observations in two diametrically opposing bone diseases: the osteoporosis and the osteopetrosis.

Osteoporosis. An intriguing theory that emerged a few years ago suggested that the constant excessive need for blood cell generation may have a role in the etiology of female osteoporosis. Post-menopausal osteoporosis occurs rapidly after the decline of estrogen production, indicating that preconditions may be already present in the female organism at its onset. Fertile women lose about 70 ml of blood every month, roughly a bit less than 1 l every year and more than 30 l by the end of their fertile life. On the basis of this simple calculation, Gurevitch

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Table 1 Major findings on the interplay between osteoclasts and hematopoiesis

Model	*Major findings*	*Reference*
Ectopic transplantation of bone marrow plug in blood-letting mice	Increased hematopoiesis Reduced bone volume	11
Ovariectomized rats	Reduced hematopoiesis with time Increased osteoclasts	16
Osteopetrotic humans and mice	Fibrotic medullary tissue in osteoclast-rich forms Hematopoietic tissue in osteoclast-poor forms	20,21 22,23
RANKL-treated mice	Increased HSC mobilization Inhibition of HSC anchorage to the niche Cathepsin K-dependent cleavage of CXCL12 Increased MMP-9 Decreased endosteal osteopontin content	24
MMP-9-deficient mice	MMP-9 required for HSC mobilization MMP-9 not required for HSC mobilization	24–26 27,28
Mice treated with strontium ranelate	Inhibition of osteoclasts Delay in recovery after bone marrow transplantation	6
Mice treatment with PGE2	Increased hematopoiesis Disruption of bone trabecular microarchitecture. Stimulation of bone resorption	29
Calcium sensing receptor-deficient mice	Reduced cellularity in bone marrow Reduced HSC content in bone marrow	31
Id1$^{-/-}$ mice	Osteoporosis Upregulation of osteoclast-specific genes Increased myeloid differentiation and HSC proliferation	33
Crebbp$^{-/-}$ mice	Exacerbated myeloid differentiation Reduced bone volume Increased osteoclastogenesis Increased levels of MMP-9	37
Bone marrow transplantation in thyroparathyroidectomized rats	Delay in hematocrit recovery Restoration upon PTH treatment	42
Treatment of mice with erythropoietin and bisphosphonates	Increased erythropoiesis Increased osteoclastogenesis blocked by bisphosphonates Oncostatin M released by erythroid cells in response to erythropoietin, which stimulates osteoclast formation	43–46
Treatment of mice with bisphosphonates	Impaired bone marrow engraftment Decrease of HSC number in bone marrow Promotion of proliferation and differentiation of hematopoietic progenitor cells Increase of HSC mobilization	48,52 49
Genetic knock-down in mice to induce osteopetrosis or osteoporosis, treatment with anti-resorptive agents	Increased HSC mobilization into the peripheral blood in osteopetrotic mice Increased HSC mobilization into the peripheral blood in mice treated with bisphosphonates or RANKL antibody Decreased HSC mobilization in osteoporotic mice Decrease of HSC number in bone marrow	50
Treatment of mice with bisphosphonates, *oc/oc* osteopetrotic mice	Impaired B cells in bone marrow Decrease in expression of CXCL12 and IL-7 Retention of B cells outside the bone marrow niche	51

Abbreviations: HSC, hematopoietic stem cell; MMP-9, matrix metalloproteinase-9; PGE2, prostaglandin E2; PTH, parathyroid hormone.

and Slavin[11] hypothesized that there is a hematological etiology of osteoporosis. They suggested that, because blood loss creates developmental pressure on the hematopoietic system, the number of hematopoietic cells increases. These include the monocyte-derived osteoclasts, which intensify resorption and sustain the extension of the space available for hematopoiesis. In support of their proposal, patients affected by hematological diseases accompanied by chronic anemia or hemophilia, or treated with anticoagulants, tend to develop osteoporosis.[12–14]

To demonstrate this theory, they used a preclinical model of ectopic transplantation of a bone marrow plug into the subcapsular space of the mouse kidney, which triggers mesenchymal progenitor cells from the transplant into the development of bone and hematopoietic microenvironment.[15] Mice were then subjected to blood-letting for 10 months (about 1/3 of their lifespan). The overall features of the ectopic ossicles developed in the chronically bled mice confirmed the assumption of the authors as they showed more hematopoiesis and less bone development compared with the ossicles formed in mice not subjected to blood withdrawal.[11] However, the results using other experimental models were not in line with this hypothesis. In fact, in ovariectomized rats, Lei *et al.*[16] observed that there is a time-dependent bone loss associated with an increase in osteoclast numbers and a parallel reduction in the volume of hematopoietic tissue. Therefore, at least in rats, these observations contradict the notion that osteoporosis is associated with an increase of hematopoiesis.[11]

Osteopetrosis. Intriguingly enough, in osteopetrosis, a condition of high bone mass and hematological failure in which osteoclasts are dysfunctional, bone marrow hematopoiesis is impaired regardless of the number of osteoclasts present in the microenvironment.[17] In both osteoclast-rich and osteoclast-poor osteopetroses, which differ for the presence of a high number of non-functional osteoclasts in the former and the total absence of osteoclasts in the latter, anemia, pancytopenia and altered blood clothing are similarly observed.[17] These events are associated with an insufficient space for hematopoietic tissue to evolve. However, recent observations showed different histological aspects in osteoclast-rich and osteoclast-poor

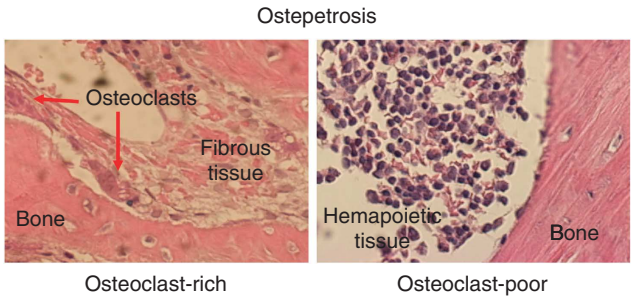

Figure 1 Hematopoiesis in osteopetrosis. Histological sections of bone biopsies of patients affected by osteoclast-rich and osteoclast-poor osteopetrosis showing abnormal fibrous tissue in the former and hematopoietic tissue in the latter. Hematoxylin/eosin

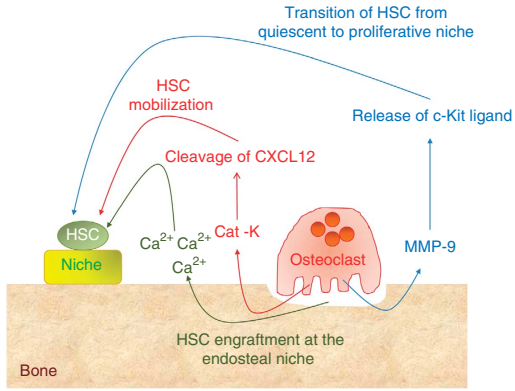

Figure 2 Role of enzymes and calcium released by osteoclasts on HSC. Cartoon showing the hypothetical role of cathepsin K (Cat-K), matrix metalloproteinase 9 (MMP-9) and calcium (Ca^{2+}) on HSC mobilization, proliferation and engraftment at the endosteal niche.

osteopetrosis.[18,19] In fact, pathological examination of the bone biopsies of osteoclast-rich osteopetrotic patients refer to 'irregular and massive primary trabeculae surrounded by abnormal fibrous tissue'.[20,21] In contrast, Sobacchi *et al.*[22] and Guerrini *et al.*[23] showed a few bone biopsies of osteoclast-poor patients, describing the presence of scant hematopoietic tissue in small medullary spaces, with, however, no fibrosis (**Figure 1**). As most hallmarks of the two forms of osteopetrosis are very similar except for the presence of high number of osteoclasts versus their absence, it is worth to hypothesize that, at least in this pathological condition, nonfunctional osteoclasts may contribute to the development of fibrosis, possibly inhibiting hematopoiesis.

Role of Osteoclast Enzymes

Osteoclasts are ectoenzyme-producing cells.[10] Cathepsin K, for example, is the major collagenolytic enzyme released in the osteoclast-resorbing lacuna from the lysosomal compartment, and Kollet *et al.*[24] suggested that osteoclast cathepsin K meditates the cleavage of an important chemokine, CXCL12, responsible for the anchorage of HSCs to the niche, causing the mobilization of immature hematological progenitor cells into the circulation (**Figure 2**). However, definitive conclusions on the role of cathepsin K in cleaving CXCL12 cannot be drawn yet because of the lack of data in suitable animal models, such as the cathepsin knockout mice.

Kollet *et al.*[24] also observed that MMP-9 contributes to the recruitment of immature progenitors to the circulation by RANKL-stimulated osteoclasts in a CXCR4-dependent manner, a condition not observed in protein tyrosine phosphatase ε-knockout mice, which have defective osteoclasts. This progenitor egress was prevented by calcitonin, a potent inhibitor of osteoclast bone resorption (**Table 2**). Finally, they observed that RANKL-stimulated osteoclasts reduced osteopontin content along the endosteum, which is considered an important component of the endosteal niche that retains the HSCs in place. Consistent with these results, Heissig *et al.*[25] have demonstrated that recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9-mediated release of c-kit ligand, which permits the transfer of HSCs from the quiescent to the proliferative niche, indirectly suggesting a role of osteoclasts in HSC niche maintenance (**Figure 2**). Finally, Pelus *et al.*[26] showed that MMP-9 is indeed involved in HSC mobilization induced by the chemokines GRO/β/CXCL2 and GROβ$_t$/CXCL2$_{\Delta 4}$, an event neutralized in neutrophil-depleted mice, which also lack MMP-9, and partially blocked by the MMP-9 inhibitor MeOSuc-Ala-Ala-Pro-Cal-CMK.

However, other studies argued against MMP-9 having any effect on HSC mobilization. Robinson *et al.*[27] and Levesque *et al.*[28] reported that MMP-9 knockout mice did not show impaired HSC mobilization, and that the engraftment of MMP-9-deficient bone marrow HSCs was not harmed in sublethally irradiated wild-type recipients. Therefore, more insights are necessary to fully understand the relevance of MMP-9 in the regulation of hematopoiesis.

Treatments

Treatment with strontium ranelate, a bone anabolic agent that increases osteoblast number but inhibits osteoclasts, has been observed to cause a delay in hematopoietic recovery after bone marrow transplantation,[6] supporting a role for osteoclastic regulation of HSCs (**Table 2**). It is also believed that prostaglandin E2 expands hematopoiesis not only by increasing HSC number but also through its complex role on the metabolism of osteoblasts and osteoclasts.[29] In fact, in mice treated with prostaglandin E2, disruption of bone microarchitecture, possibly due, at least in part, to activation of bone resorption,[30] was observed along with an increase of Lineage$^-$Sca-1$^+$c-Kit$^+$ (LSK) bone marrow HSCs[29] (**Table 2**).

Role of Calcium

It is known that the activity of osteoclasts elevates the local and systemic calcium ion concentration, and recent studies have demonstrated that the HSC engraftment at the endosteal niche is specified by the calcium-sensing receptor (**Figure 2**). In fact, Adams *et al.*[31] have shown reduced cellularity and HSC content in the bone marrow of calcium sensing-receptor-deficient mice. In these mice they also observed an increased mobilization of progenitors, suggesting that calcium may have a relevant role in keeping HSC localization in the bone marrow.

Genetic Studies

Genetic studies have attempted to demonstrate the molecular mechanisms whereby osteoclasts modulate hematopoiesis. For instance, the *inhibitor of differentiation* gene (*Id1*), a transcriptional

Table 2 Effects of bone seeking drugs on HSC and hematopoiesis

Drug	*Effect on HSC and hematopoiesis*	*Effect on bone*	*Reference*
Calcitonin	Inhibits egress of HSC from bone marrow	Inhibits bone resorption	24
Strontium ranelate	Delay hematopoietic recovery after HSC transplantation	Stimulates osteoblasts Inhibits osteoclasts	6
PGE2	Expands hematopoiesis Increases HSC in bone marrow	Stimulates bone resorption	29
Erythropoietin	Expands erythropoiesis Induces oncostatin M release	Induces bone loss	43–46
PTH	Improves hematocrit Increments HSC in bone marrow Improve HSC engraftment after transplantation	Given intermittently stimulates osteoblasts Given continuously stimulates osteoclasts	42,53
Bisphosphonates	Reduce HSC in bone marrow Impair HSC engraftment after transplantation Abolish PTH-induced HSC increment in bone marrow Promote proliferation and subsequent differentiation of progenitors Increase HSC mobilization to circulation Decrease numbers of B cells in bone marrow	Induce osteoclast apoptosis Reduce bone resorption Block erythropoietin-induced bone loss	48–52
Anti-RANKL antibody	Increases HSC mobilization to circulation	Inhibits osteoclast formation	50

Abbreviations: HSC, hematopoietic stem cell; PGE2, prostaglandin E2; PTH, parathyroid hormone.

regulator that prevents basic helix–loop–helix transcription factors from binding the DNA,[32] has been found to link bone homeostasis and hematopoiesis (**Figure 3**). In fact, *Id1*$^{-/-}$ mice showed an osteoporotic phenotype, with the osteoclast-specific genes, cathepsin K, tartrate-resistant acid phosphatase, and osteoclast-associated receptor upregulated, while the same genes were repressed in osteoclasts overexpressing *Id1*.[33] The hematopoietic compartment of *Id1*$^{-/-}$ mice showed an increase in myeloid differentiation and HSC proliferation, suggesting that in the absence of Id1 the HSCs are driven towards myeloid differentiation. Id1 has therefore been indicated as a factor in the dynamic cross-talk between osteoclasts and HSCs,[33] although further work is necessary to confirm this hypothesis.

A recent report has shown that the CREB (cAMP response element-binding)-binding protein (CREBBP), which regulates the hematopoiesis by a HSC-intrinsic effect, has a pivotal role also in the microenvironment-mediated regulation of hematopoiesis.[34] CREBBP is a coactivator of transcription that interacts with transcription factors and acetylates histones and other proteins. In humans, chromosomal translocations involving the *CREBBP* gene have been reported in leukemia[35] and myelodysplastic syndromes.[36] Defects in *Crebbp*$^{-/-}$ HSCs include impaired self-renewal and exacerbated myeloid differentiation,[37] with a tendency of *Crebbp*$^{-/-}$ mice to develop hematological malignancies with age.[38] It has been observed that *Crebbp*$^{-/-}$ mice not only poorly support HSCs, promoting excessive myelopoiesis and reducing lymphopoiesis, but also show reduced bone volume due to increased osteoclastogenesis (**Figure 3**). Interestingly, *Crebbp* deficiency in the bone marrow microenvironment results in reduced levels of MMP9, a metalloproteinase abundantly expressed in osteoclasts.

Role of Bone Marrow Monocytic Cells

Monocytes share with osteoclasts the same origin from the granulocyte/macrophage colony-forming unit. Therefore, in the context of the regulation of hematopoiesis, they may contribute to the HSC niche with mechanisms that, at least in part, may overlap or complement those employed by the osteoclasts.

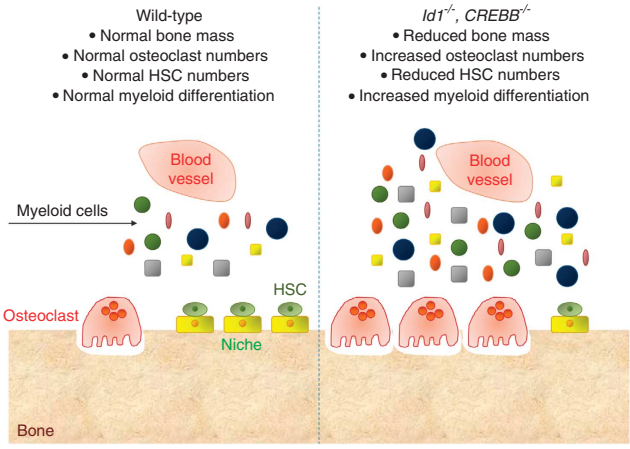

Figure 3 Genetic studies. Cartoon illustrating the effect of deletion in mice of the *Id1* and the *CREBB* genes on bone mass and myelopoiesis.

Winkler *et al.*[39] showed that administration of granulocyte colony stimulating factor (G-CSF) depleted the endosteal surface of both endosteal osteoblasts and endosteal macrophages, denominated osteomacs, which was concomitant with the HSC mobilization. Osteomacs could be pivotal in HSC egress because their depletion in Fas-induced apoptosis transgenic mice or by administration of chlodronate-loaded liposomes reduced trophic cytokines at the endosteum and HSC mobilization upon G-CSF administration. The effect of G-CSF appeared to be mediated by the restriction of G-CSF receptor to the monocytic lineage, which was depleted in the bone marrow when the cytokine was administered.[40] It is likely that one of the mechanisms underlying the role of monocytic cells in the HSC niche is the production of yet-to-be identified factors that support osteoblasts *in vivo*, although a direct evidence that this is related to the HSC niche is still lacking. In conditional depletion models of bone marrow mononuclear phagocytes, the expression of CXCL12 was found to be diminished, contributing to HSC egress. Consistently, in this model, the response to CXCR4 antagonists and to G-CFS was enhanced.[41]

Role of Erythropoietin

In 1971, Perris *et al.*[42] had reported an association of the bone marrow response with acute bleeding due to hypocalcemia and release of PTH, observing a delay of hematocrit recovery in thyroparathyroidectomized rats compared with controls, and a restoration upon PTH infusion (**Table 2**). These observations suggest a close relationship between erythropoiesis and bone resorption.

Erythropoietin is the major physiological cytokine that supports erythropoiesis. Factors released by erythroid cells in response to this hormone regulate the osteoblast/osteoclast coupling. Erythropoietin stimulates osteoclastogenesis in the first instance, followed by an increase in osteoblastogenesis that is induced either by erythropoietin directly or through the expression of bone morphogenetic proteins 2 and 6 by HSCs through the Jak/Stat signaling.[43] Oncostatin M, a member of the gp130 family of cytokines, is also induced strongly in erythroblasts in response to erythropoietin.[44] Oncostatin M binds to and signals the osteoblasts to produce RANKL, subsequently inducing osteoclast differentiation[45] (**Table 2**). Therefore, oncostatin M contributes to the orchestrated response of erythroid cells to erythropoietin and to the changes in the local bone structures and osteoclast response. Consistent with this knowledge, mice treated with a clinically relevant dose of erythropoietin showed a rapid loss of the trabecular bone volume. Interestingly, bisphosphonates blocked the erythropoietin-induced bone loss and the magnitude of the erythroid response to erythropoietin,[46] once again suggesting a close association between bone resorption and myelopoiesis. In fact, the article points to the interplay between erythroid development and skeletal homeostasis, suggesting that bone remodeling is required for attaining sufficient bone marrow space for erythroid expansion. This has been proposed by Suda[47] to reflect the phylogenic process of bone marrow formation within the bone cavity.

Anti-resorptive Drugs

Recent papers have directly addressed the importance of osteoclast activity in the context of the regulation of hematopoiesis, with, however, contradictory results (**Table 2**). Lymperi *et al.*[48] showed that inhibition of osteoclast function reduces HSC numbers *in vivo*. To address this question, they tested the effects of bisphosphonates on hematopoiesis, and observed that mice treated with bisphosphonates displayed a drop in HSCs in the bone marrow. They also observed impairment of the engraftment of bone marrow cells harvested from treated animals. Bisphosphonates also abolished the HSC increment produced by PTH, confirming that this hormone acts on hematopoiesis, at least in part, through the enhancement of osteoclast activity. They also observed that a larger fraction of LSK cells in the bone marrow of treated mice entered the cell cycle, suggesting that osteoclast impairment promotes proliferation and subsequent differentiation of progenitor cells, a finding in line with the observations in the *Id1*$^{-/-}$ and the *Crebbp*$^{-/-}$ mice.[32,33] HSC impairment was considered a consequence of niche manipulation, because the bone marrow from untreated donor mice transplanted into mice previously treated with bisphosphonates showed a delay in hematopoietic recovery compared with untreated controls. Therefore, the authors concluded that osteoclast function is fundamental for the maintenance of a correct HSC niche.[48]

In a previous work, however, Takamatsu *et al.*[49] had found that short-term G-CSF administration increased bone resorption concomitant to the egress of HSC. In this circumstance, the bisphosphonate pamidronate reduced the G-CSF-induced bone resorption but, instead of decreasing, it increased the number of HSCs mobilized from bone marrow, suggesting that bone resorption is not the direct cause of HSC mobilization but rather a parallel event.

Miyamoto *et al.*[50] performed an elegant study using various models of osteoclast-deficient mice and also concluded that osteoclasts are dispensable for HSC maintenance and mobilization. They caused HSC mobilization in mice by sequential treatments with G-CSF and counted the number of LSK cells in the peripheral blood. They observed that mobilization of HSCs from bone marrow was increased in bisphosphonate- or RANKL antibody-treated mice compared with controls. Likewise, the number of HSCs mobilized into the blood was higher in mice with osteopetrotic genotypes, including the macrophage colony stimulating factor-, RANKL- and c-Fos-deficient mice. Consistently, mice deficient in the anti-osteoclastogenic cytokine osteoprotegerin, whose phenotype is characterized by increased numbers of osteoclasts and exacerbated bone resorption, exhibited reduced HSC mobilization, leading the authors to conclude that osteoclasts prevent HSC mobilization and may be negative regulators of the hematopoietic system.[50] It is worth noting, however, that, according to the involvement of monocytic phagocytes in the regulation of the HSC niche,[39–41] drugs disrupting osteoclasts could also trigger a positive feedback loop that could affect the homeostasis of bone marrow macrophages through their myeloid progenitors.

A recent report suggested that bone marrow B lymphopoiesis is also regulated by osteoclast activity. Osteopetrosis was induced in normal mice by injections of zoledronic acid, which caused B-cell number to decrease specifically in the bone marrow. This effect was due to a decrease in the expression of CXCL12 and IL-7 by stromal cells, which led to retention of B-cell progenitors outside of the bone marrow niches. Similar results were observed in the osteopetrotic *oc/oc* mice, suggesting that they were not due to the zoledric acid itself but to the microenvironmental condition created by reduced osteoclast activity.[51]

Lastly, a very recent paper suggested that osteoclasts promote the formation of the HSC niche by controlling the maturation of osteoblasts.[52] In *oc/oc* mice and in wild-type mice treated with zoledric acid, the frequency of LSK cells in the bone marrow decreased by >90%, whereas that of mesenchymal progenitors increased to 80% of the total number of bone marrow cells compared with 20% in wild-type untreated mice. These mesenchymal progenitors were not capable of recruiting LSK cells and their differentiation into the osteoblast lineage was impaired, suggesting that osteoclasts could affect HSC niche development through their influence on osteoblast differentiation.

Clinical Considerations

From this set of data, it is clear though that the field is rapidly expanding, but that a consensus on the role of osteoclasts and bone resorption in the regulation of hematopoiesis is not yet possible because of the heterogeneity of observations and experimental data. However, some considerations can be drawn, especially in the clinical context because treatments

with current bone-seeking drugs may have implications on the well-being of patients with hematological failures. For instance, bisphopshonates have been shown to suppress HSC in the bone marrow[48,52] and to increase its mobilization into the peripheral blood.[48,50] This may implicate that caution must be used for the engraftment of bone marrow when anti-resorptive drugs are used, but could also implicate that treatment with anti-resorptive drugs could improve the yield of HSCs from the peripheral blood of donors in which HSC mobilization is enhanced by treatment with G-CSF for transplantation purpose. Likewise, it is established since the pioneer paper by Calvi *et al.*[53] that PTH increments HSC number in the bone marrow and enhances the engraftment of transplanted HSCs, a finding that has been confirmed more recently by various studies.[2] Therefore, administration of PTH can be envisioned as a potential treatment of both donors and hosts to improve the HSC yield in the former and their engraftment in the latter. These implications could be highly relevant also in case of autologous transplant in patients affected by multiple myeloma, a disease that presents with serious bone involvement often treated with anti-resorptive therapy.

In osteopetrotic patients subjected to bone marrow transplantation, a frequent adverse effect due to the appearance of functional osteoclasts is the development of hypercalcemia, for which patients are treated with anti-resorptive drugs.[54] It is already known that caution must be used for the treatment of infants with these drugs as they can greatly affect bone turnover with consequences on bone quality. The studies available so far indeed suggest that even more caution is needed as inhibition of bone resorption may also worsen the engraftment and maintenance of HSC, thus compromising the beneficial effects of bone marrow transplantation. Similarly, children with osteogenesis imperfecta or other diseases characterized by severe bone loss are often treated with bisphosphonates.[55] Concerns have been raised on the long-term use of bisphosphonates in childhood because, by blocking the bone turnover, they are known to cause a paradoxical bone fragility later in life.[56] There is now an additional concern as these kids should probably be monitored also for hematological failures in the light of the putative negative role of osteoclast inactivity on HSC maintenance in bone marrow.

Finally, the regulatory nexus between erythropoietin administration and bone remodeling may also have important clinical implications, for example, in explaining the skeletal deformities in β-thalassemia, which is characterized by increased erythropoietin production. Likewise, patients affected by renal failure are treated with erythropoietin, which may have an impact on their severe osteodystrophy. Moreover, excess of erythropoietin administration in preparation of autologous blood transfusion may have implications, for instance, in patients affected by leukemia or multiple myeloma, considering the serious bone complications observed in these onco-hematological diseases.[47]

Conclusions

In conclusion, this rapidly expanding field of research is likely to shortly address new questions on the role of osteoclasts in the regulation of hematopoiesis and on the underlying molecular mechanisms. It is necessary though to monitor the new findings, trying to unequivocally clarify whether active osteoclasts are an advantage or a disadvantage for HSC maintenance, mobilization and progression towards myelopoiesis, especially in the clinical context.

Conflict of Interest

The author declares no conflict of interest.

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