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MOLECULAR BIOLOGY OF BONE METASTASIS (H TAIPALEENMÄKI, SECTION EDITOR)

Bone Marrow Niche: Role of Different Cells in Bone Metastasis

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Abstract

Purpose of Review This report summarizes current knowledge of bone marrow hematopoietic stem cell (HSC) niche, focusing on the identification of niche cells and molecular mechanisms involved in HSC maintenance and bone metastasis.

Recent Findings Novel imaging techniques are greatly improving our understanding of bone marrow niche and latest studies have revealed several complex multicellular regulatory mechanisms of niche function. Especially, the intriguing role of bone marrow macrophages and osteomacs is an emerging topic in the field. It appears that, e.g., macrophage polarization is important for communication with bone marrow stromal cells (BMSCs). Bone marrow is also a favorable environment for disseminated tumor cells and recent data shows that various niche cell types, including endothelial cells and BMSCs, regulate the progression of bone metastasis.

Summary Bone marrow niche represents a multicellular system with complex interactions. Emerging data is providing us with a deeper understanding of this fascinating tissue and its role in metastasis.

Keywords Bone marrow niche · Hematopoietic stem cells · Bone marrow stromal cells · Myeloid cells · Bone metastasis · Disseminated tumor cells

Introduction

A niche is defined as a local tissue microenvironment that maintains and regulates a particular type of stem or progenitor cells. Bone marrow (BM) is known to produce and nurture multiple stem cells and has thus been considered as a good model for a niche. Actually, the presence of hematopoietic stem cell (HSC) niche in BM was suggested already in 1978 [1]. The idea was further pursued by analyzing the capacity of BM stromal cells (BMSCs) to maintain the primitive hematopoietic cells ex vivo [2] and in vitro studies with cultured human cells further fostered the idea that bone cells support HSCs [3]. However, due to technical limitations at the time, HSC localization in BM was not verified until the 2000s when genetically engineered mouse strains allowed to test this hypothesis in vivo. Studies indicated that osteogenic lineage cells could regulate stem cells in vivo but it remained unclear whether the effect was direct or indirect.

Currently, two anatomically distinct microenvironments, i.e., perivascular and endosteal niches, have been defined. Perivascular niche is located around the bone marrow sinusoidal vessels in the central marrow cavity. It is characterized by actively dividing HSCs, as well as sinusoidal endothelium, BMSCs, and C-X-C motif chemokine 12 (CXCL12, also known as SDF-1) abundant reticular cells (CARs) (Fig. 1). Endosteal niche is in turn located at the lateral compartment of the BM endosteal space and is more defined by the presence of BMSCs and other osteoblastic cells forming the stroma. Here, these cells as well as bone-resorbing osteoclasts are interacting with stem cells (Fig. 1). It also acts as the site for early lymphoid cell development.

Bone, or bone marrow, is a significant target organ for metastasis. It provides a fertile soil for disseminated tumor cells (DTCs). Especially prostate cancer (PCa) and breast cancer (BrCa) are preferentially known to invade BM. Recent discoveries have demonstrated that there are distinct tumor promoting milieus, such as pre-metastatic and metastatic niches in various tissues and organs [4], and it seems that DTCs from primary tumors can commandeer this supportive

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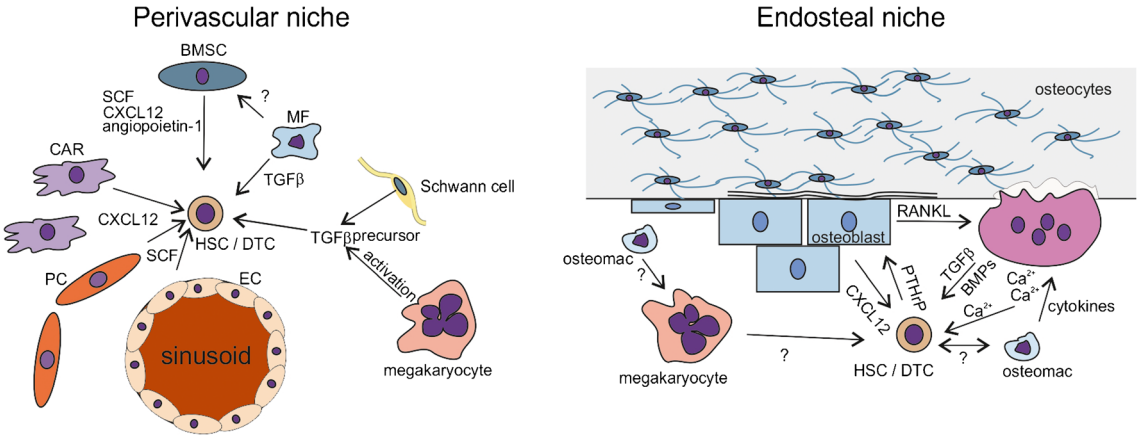

Fig. 1 Bone marrow perivascular and endosteal niches. Multiple cell populations have been characterized to influence the function of the perivascular niche, which can be populated by HSCs or by DTCs. CARs are probably the most important sources of CXCL12, which is vital for maintaining the niche. In addition, pericytes (PC), endothelial cells (EC), and BMSCs secrete other important niche factors, such as SCF and angiopoietin-1. Macrophages (MFs) have been shown to be a source for TGFβ, which can maintain HSC dormancy. Currently, the regulatory mediators between the interactions between MFs and BMSCs are incompletely known. As an example of multi-cellular regulation of HSCs, Schwann cells are also suggested to secrete TGFβ precursor, which can then be activated by proteases secreted by megakaryocytes. At the endosteal niche, the relative significance of osteoblast-secreted CXCL12 is higher when compared to the perivascular niche. A classical "vicious cycle" can be formed by a PTHrP-secreting DTC which induces osteoblasts to secrete RANKL leading to enhanced maturation of osteoclasts and subsequent release of matrix-bound TGFβ and BMPs. Bone resorption by osteoclasts increases local extracellular calcium concentration, which can have direct effects on HSCs. A multicellular regulation of endosteal niche by osteomacs and megakaryocytes has been suggested, but the exact molecular mechanism is not known

microenvironment. In BM, DTCs may adapt to and alter a pre-existing HSC niche for their survival and growth into metastases. While the endosteal osteoblastic niche is the preferential site for invading PCa cells [5, 6], recent reports implicate that the perivascular niche would regulate the dormancy of disseminated BrCa cells [7, 8], suggesting that diverse bone marrow niches can serve as sites for not only malignant growth but also as sources of potential relapse. Nevertheless, the bone marrow niche and its role in metastasis development still remain incompletely understood.

Identification of Adult Bone Marrow Niche

Identification of BM niche in vivo has been challenged by technical limitations. Even though the method to analyze hematopoietic cells by flow cytometry has long been available [9], the same antibodies are not always applicable for complex immunostaining of bone tissue sections. As a consequence, non-specific markers, such as 5-bromodeoxyuridine or GFP-labeled histone H2B, have been used [10, 11] with inconclusive results.

One breakthrough in early 2000s was the discovery of SLAM (signaling lymphocyte activation molecule) family markers, which were differentially expressed between HSCs and other hematopoietic precursors. HSCs were demonstrated to localize next to the sinusoidal blood vessels in murine BM and spleen [12]. This was later confirmed by others using different combinations of HSC markers [13–15]. Importantly, advanced confocal imaging confirmed that indeed the majority of HSCs was associated with sinusoidal blood vessels [16] and thus, the existence of perivascular HSC niche in adult bone marrow was verified. However, it has recently been shown that many of the potential HSC niches are not occupied by HSCs during normal hematopoietic homeostasis in adult mouse [17•].

Utilization of inducible cell-type specific promoters to turn on fluorescent protein expression has been an excellent tool for niche cell characterization in vivo [13, 18••]. This, together with the development of multi-photon confocal microscopy, has allowed 3D imaging of tissue samples and the detection of fluorescent cells therein. A novel method to process bone tissue samples as optically transparent but simultaneously retaining the fluorescent properties of the resident cells may enable easier in vivo characterization of BM niche cells in the future [19•].

Very recently, the spatial distribution of bone and BM structures, including extracellular matrix (ECM) and non-hematopoietic cells in mouse whole femora, was comprehensively evaluated by advanced 3D imaging [18••]. These results now provide an atlas for the distribution of over 40 markers for cells of osteoblastic, vascular, perivascular, neuronal, and stromal lineages, as well as for ECM proteins, and can be widely utilized in the forthcoming research.

It should however be noted that despite of the great technical progress in the identification on BM niche and its components, the current in vivo methodologies can only be applied in experimental animals. There is detailed understanding of the murine HSC niche but the data on key cells and molecular players controlling human niche function remains limited. However, HSCs and other niche-related cells have been analyzed in human samples ex vivo, e.g., by flow cytometry, immunohistochemistry, and in vitro cell cultures. In vitro co-

culture models have provided information on the key cell populations supporting human HSCs and similarly to mouse, these include endothelial cells (ECs), BMSCs, and osteoblastic cells [20]. In addition, advanced 3D co-culture systems using various combinations of purified niche cells are being developed to better recapitulate interactions in human BM [21]. Evolving data implicates that there are many similarities between mouse and human HSC niche composition and function but since human HSCs are different from mouse, it is likely that human niche also has unique features that are not reflected in mouse models.

Bone Marrow Niche Cells Supporting HSCs and Implications in Bone Metastasis

Current data indicates that there are specialized niches for different types of HSCs and progenitors in healthy adult bone marrow and that the multiple cell types can have both unique and redundant functions within these niches. Early approach to identify the essential cells was the ablation of certain cell populations by utilizing mouse models where conditional expression of, e.g., herpesvirus thymidine kinase or diphtheria toxin receptor was induced in specific cells. Various cell populations, such as osteoblasts [22] as well as megakaryocytes [23, 24] and macrophages [25, 26], were depleted from the bone marrow and in each case, HSCs were either activated or their numbers reduced. However, like in any interactive system, the effects can also be indirect. It is therefore not fully clear if, e.g., the effects of osteoblast ablation are direct or whether they are related to some other type of niche-independent injury response.

The "seed and soil" concept of metastasis that was described by Stephen Paget over a century ago [27] is consistent with recent studies, which have demonstrated that the communication between DTCs and niche components is crucial for metastatic progression [28]. It is now known that malignant cells indeed hijack BM niche [29]; for example, PCa and BrCa utilize similar mechanisms as HSCs in their homing to bone marrow [30, 31]. The niche supports DTCs but they can also themselves remodel niche components for a further benefit. Thus, studying both the cellular and molecular mechanisms of a normal, "healthy" niche and the crosstalk between malignancy and BM microenvironment are currently of great interest. Below, we discuss the present knowledge on various cell types supporting the HSC niche and their potential roles in the progression of pre-metastatic BM niches into metastases.

Osteoblasts, HSC Niche, and Bone Metastasis

Osteoblasts are the predominant cell type along the endosteum and it was earlier anticipated that they could interact with HSCs at the endosteal niche. This hypothesis was tested with genetically manipulated osteoblastic cells but no acute effect on HSC frequency was detected [22, 32]. Furthermore, more recent studies have demonstrated that only a few HSCs reside at the endosteal surfaces [16] and that osteoblasts do not express the crucial stem cell factor, SCF [33]. Therefore, it seems that osteoblasts do not directly promote HSC maintenance but can rather have indirect effects on HSCs.

Along the same lines, the relevance of osteoblasts in promoting and/or maintaining the BM metastatic niche is not fully clear. There are studies showing that PCa cells target the same osteoblastic nice as HSCs do [5] and that PCa-derived cells potentiate BM myeloid cells via parathyroid hormone-related protein (PTHrP) to upregulate the expression of, e.g., vascular endothelial growth factor A (VEGF-A) and interleukin 6 (IL-6) in osteoblasts, thus contributing to tumor growth and angiogenesis [34]. Interestingly, the prometastatic cytokines were also shown to stimulate osteoblasts to produce more VEGF-A and IL-6, suggesting that osteoblastic cells may amplify the effects of immune cell-derived cytokines in bone microenvironment. Based on the current literature, it appears to be experimentally challenging to distinguish direct vs. indirect effects in vivo. In addition, part of the observed effects regarding osteoblasts may actually be mediated by osteoprogenitors or their earlier precursors, such as BMSCs.

Bone Marrow Stromal Cells, HSC Niche, and Bone Metastasis

Primitive osteogenic precursors located at the metaphyseal area not only in adult but also in fetal and early postnatal BM have been implicated in maintaining the HSC niche. These cells form fibroblastic colonies and undergo multilineage differentiation in vitro [35]. The term "mesenchymal stem/stromal cell" (MSC) is currently used generally for primary cultures of fibroblastic cells from various tissues or organs, having substantial plasticity and multilineage differentiation potential [36, 37]. The term MSC was in fact first introduced to refer to cultures of BM-derived MSCs [38, 39] but to date, evidence from rigorous assays indicates that BMSCs specifically include stem cells for skeletal tissues.

BMSCs are among the stromal cells that secrete HSC niche factors in the adult BM and that may also regulate the niche formation during development. CD146+ BMSCs have been demonstrated to localize around sinusoids and to synthesize various factors associated with HSC niche, such as angiopoietin 1, SCF, and CXCL12 [40]. However, there still are many open questions of the role of BMSCs in HSC maintenance. The BMSC population producing HSC niche factors is highly heterogeneous and it can be anticipated that only a subset of these cells are true BMSCs. Major issue relates to the localization of BMSCs, since they seem to prefer the metaphyseal area [41, 42], where they are not necessarily associated with HSCs.

The role of BMSCs in maintaining the metastatic niche originates from the observations that PCa and BrCa cells have

the potential to adopt the properties of osteoblast lineage cells. This phenomenon, osteomimicry, is thought to be the key feature of metastatic capacity and has been very recently reviewed [43]. Since osteoblasts are of mesenchymal origin, these phenotypic changes likely occur in a tumor cell that has already undergone the epithelial-mesenchymal transition (EMT), a fundamental step for tumor cell migration and invasion of distant organs. BMSCs have indeed been shown to promote the growth of various cancer types as well as to associate with the cancer sites. Since BMSCs locate to tumors, there have been some attempts to utilize this capacity to modify these cells to act as cargo for the drug delivery [44], but due to treatment concerns, such approaches have not been tested clinically.

Interestingly, it has been shown that BMSCs can transform into cancer-associated fibroblasts (CAFs) within the primary tumor [45, 46]. The mechanisms involve various chemokine ligand-receptor axes, indicating that BMSC-derived CAFs may utilize the same mechanisms as stem cells in their activities. Furthermore, BMSCs may also be involved in establishing the DTC dormancy, which according to recent reports can be mediated by BMSC-derived exosomes [47]. Breast cancer cells were lately shown to prime BMSCs to release exosomes with distinct miRNA contents, which in turn promoted quiescence in a subset of cancer cells and conferred drug resistance [48]. The role of BMSCs in tumor development from growth of the primary tumor to the establishment of distant metastasis has recently been reviewed in detail [49].

Endothelial Cells, Pericytes, HSC Niche, and Bone Metastasis

The localization of HSCs next to the blood vessels indicates that endothelial and perivascular cells could maintain the perivascular niche. Endothelial cells (ECs) have been shown to promote HSC maintenance [50] and self-renewal and repopulation in vitro [51]. Other important cells for niche function include perivascular stromal cells (pericytes) and CAR cells, both of which most likely belong to the same perivascular compartment. The significance of sinusoidal ECs, pericytes, and CAR cells in the niche maintenance is emphasized by the fact that they are the main source of CXCL12 compared to the relatively low levels produced by osteoblasts. CAR cells, originally described by Nagasawa and his colleagues [13], express CXCL12 at 100–1000-fold higher levels than endothelial and osteoblastic cells, respectively. In addition, ECs and pericytes are the main source of SCF, a critical survival and growth factor for hematopoiesis.

During invasion and migration, circulating tumor cells have constant contact with endothelial cells and pericytes as they must intravasate and extravasate the blood vessel to reach the secondary site. In addition to the increased vascular permeability, increased angiogenesis is also needed for a pre-metastatic niche to promote metastasis. Endothelial cells in the pre-metastatic niche have indeed been shown to produce VEGFs and other proangiogenic factors to create a metastasis-promoting microenvironment, especially in lymph nodes [52] and recent evidence shows that blood vessels also contribute to bone metastasis. ECs of BM blood vessels express high levels of CXCL12 in specific local areas, attracting metastatic tumor cells that express high levels of the CXCL12 receptor, i.e., C-X-C chemokine receptor 4 (CXCR4) [53]. Interestingly, dormant breast cancer cells were demonstrated to localize near the stable BM microvasculature and perivascular cells secreting thrombospondin-1. When angiogenesis was stimulated, ECs started sprouting and limited the secretion of thrombospondin-1 but induced the expression of e.g. transforming growth factor beta 1 (TGFβ1), which stimulated the DTCs to get out of their quiescent state and start colonizing the bone [8]. On the other hand, lung ECs have been shown to produce pro-inflammatory cytokines S100A8 and S100A9 to recruit myeloid cells to niche and initiate the pre-metastatic cascade [54], suggesting that possibly a similar mechanism could also be relevant in bone metastasis.

Osteomacs, HSC Niche, and Metastasis

Macrophages originate either from circulating monocytes (as response to inflammation), formed from bone marrow common monocyte progenitors [55] or from embryonic yolk sac [56]. Macrophages found in BM but unassociated with endosteal surfaces are usually nominated as bone marrow macrophages. The phenotypic differences of these cell populations are not yet fully characterized, but at least Mohamad et al. define BM macrophages as CD166 negative [57••]. Osteomacs are BM-resident cells displaying murine macrophage surface markers, such as Mac-3 and F4/80, but low levels or no Mac-2 [57••, 58, 59•] and co-express CD166 and M-CSFR [57••]. By definition, osteomacs should reside within three cell diameters from nearest bone tissue [60] and they are often found in association with osteoblastic cells both in periosteal and endosteal compartments [59•, 61]. Currently, the origin of osteomacs has not been studied in detail. In contrast to osteoclasts, they do not express (or express very little) tartrate-resistant acid cellular phosphatase (TRAcP) and are not multinucleated [25, 58].

Macrophages can adapt to environmental signals with a spectrum of activation stages: the extremes being inflammatory M1 polarization (classical activation) and anti-inflammatory M2 polarization [62, 63]. The latter is divided to three subclasses (M2a, b, c) in human histology analysis [62, 64]. Little is known on the role of osteomac polarization in BM niche function or osteomac polarization per se, even though generally macrophages are involved in regulation and maintenance of the BM niche [25, 26]. More recent studies have described different subsets of macrophages regulating HSC maintenance and dormancy. For example, α-smooth muscle actin positive activated monocytes and macrophages

can maintain HSCs and protect them during stress conditions [65], while a subset of macrophages expressing Duffy antigen receptor for chemokines (DARC) retain HSC dormancy via TGFβ-Smad signaling [66••].

Macrophages reside in the vicinity of Nestin-positive BMSCs, known to express factors retaining HSCs and in turn, macrophages could also communicate with the BMSCs via incompletely known mechanisms [67]. Interestingly, different effects of M1 and M2 polarized macrophages on BMSCs have recently been demonstrated in vitro, where M1 macrophages amplified T cell immunosuppression by BMSCs in a contact-dependent CD54-mediated manner, while the effects mediated by M2 macrophages were contact-independent [68••]. Furthermore, specific sets of macrophages have been demonstrated in the endosteal and perivascular HSC niche and perivascular BMSC niche [67, 69]. A recent study by Mohamad et al. demonstrated that the capacity of osteoblasts to potentiate hematopoiesis was enhanced in co-culture with osteomacs derived from calvarial bone, whereas bone marrow (endosteum)-derived macrophages did not mediate such an effect. Furthermore, megakaryocytes were in turn shown to augment this activity [57••]. Thus, a multicellular network including at least osteoblasts, osteomacs, BMSCs, and megakaryocytes is likely to form a complex system regulating the resting and proliferation of HSCs.

Little is known of the role of osteomacs (by their strict definition) in bone metastasis. However, bone marrow macrophages have been shown to participate in bone metastasis growth. In mouse model of PCa bone metastasis, the resident BM macrophages associated with the growing lesion were shown to express M2-type surface markers (e.g., CD206) [70•]. Furthermore, by using a mouse metastatic PCa model in conditionally macrophage-depleted MAFIA mice, the elimination of bone resident macrophages was shown to significantly reduce lytic bone lesion growth and serum TRAcP5b levels without significantly affecting the amount of osteoclasts [70•]. The bone volume was also reduced which is in line with the suggested macrophage support for osteoblasts by Mohamad et al. [57••].

Niche and Metastasis Regulation by Other Cell Types

Besides the cells described above, also, other cell types in the BM environment regulate HSC niche by SCF and CXCL12-independent mechanisms and can also potentially participate in metastatic progression. These cells include megakaryocytes, nerve cells, and osteoclasts. Megakaryocytes modulate HSCs e.g. by expressing TGFβ, which promotes HSC quiescence in vivo [71]. Nerve fibers and Schwann cells have also been shown to control HSC function by multiple mechanisms. Nerve fibers regulate the circadian release of HSCs from BM into circulation [72] and the non-myelinated Schwann cells regulate the proteolytic activation of TGFβ and thereby promote HSC maintenance [73]. Interestingly, TGFβ is one of the growth factors that has been shown to remodel lung parenchyma for metastatic niche formation [54] and, in parallel, TGFβ could be a potential mechanism for the establishment of bone metastatic niche.

There is data indicating that besides macrophages, also other cells of the monocyte lineage, such as osteoclasts, can control HSCs. Osteoclasts residing on the endosteal surface may modulate HSC function by the release of Ca2+ and bone matrix embedded growth factors during bone resorption [74, 75]. HSCs express calcium sensing receptor (CaSR) and interestingly, even though mice deficient in CaSR have normal fetal hematopoiesis, their BM colonization by HSCs is very low [76]. This indicates that local endosteal Ca2+ concentrations can play a role in HSC niche establishment and maintenance. Various growth factors, such as TGFβ, insulin-like growth factors (IGFs) and bone morphogenetic proteins that are released from the bone matrix during bone resorption induce bone formation but are also involved in HSC regulation. The role of osteoclasts in the formation and maintenance of HSC niche, as well as HSC mobilization, has been recently reviewed [77].

Breast, prostate, and lung cancer have a preference to metastasis to bone [78] and the mechanisms enabling the "vicious cycle" of osteolytic bone lesions are well-studied. Cancer cells secrete factors such as PTHrP which stimulate osteoclast-mediated bone resorption through the RANK/RANKL/OPG signaling pathway. On the other hand, diverse growth factors released by resorbing osteoclasts (see above) further stimulate tumor growth and the production of tumor-derived factors (such as PTHrP), thus creating a vicious cycle (for a review, see [43]). Osteoclasts can affect niche components and metastasis both via indirect effects on osteoblasts and BMSCs and direct effects on HSCs and cancer cells. A recent study described a dichotomous role for DKK1 signaling in BrCa metastasis formation [79••]. DKK1 signaling was found to reduce cancer cell lung metastasis via inhibiting macrophage and neutrophil recruitment to the metastasis site, while in bone cancer, cell-derived DKK1 augmented osteoclast activity via suppression of OPG formation by osteoblasts. This effect on osteoclasts led to increased lytic metastasis formation in bone. In a recent study, osteoclast-derived arachidonic acid was shown to be a powerful chemoattractant for BrCa cells, whereas lysophosphaditylcholines inhibited cancer cell proliferation and survival [80••]. Thus, an altered osteoclastic lipid secretome is a new mechanism promoting bone metastasis formation in mice.

Conclusion

Complexity of niche is reflected by the fact that instead of a single cell type, there is a system, where the functions of multiple participants are integrated. Furthermore, the system is not static

but can change as a response to stress or under different physiological conditions. It is unclear how pharmacologically modulating one niche component would affect the other cell types within the BM microenvironment. Deleting a single molecule in a single niche cell population is not always robust. There is redundancy and compensation from other cell types producing the same factor, thus making the pharmacological therapies targeting the BM niche and metastatic progression very challenging.

It is now well established that niches are different depending on their anatomical location and the cellular composition is reflected by that. As different cancer types have an obvious preference to spread DTCs to different niches, therapies to mitigate the DTCs in bone marrow probably need to be tailored accordingly. Bone marrow niche components can be modulated by invading tumor cells, which utilize the intrinsic molecular and cellular mechanisms for their own benefit. The various cellular players regulate each other via secreted cytokines, chemokines, growth factors and exosomal miRNAs. Many of the molecular mechanisms between e.g. tumor macrophages and cancer cells have been characterized in soft tissue tumors but how they translate to interactions between DTCs and osteomacs—and the relative significance of different macrophage populations in BM in general—is calling for further studies. The recent observations on the indirect regulatory effects on HSCs by e.g. Schwann cells and megakaryocytes show that currently focus of the research on the cellular regulation of the niche is already moving to more distal populations from the previously characterized populations.

Compliance with Ethical Standards

Conflict of Interest Terhi J. Heino and Jorma A. Määttä declare no conflicts 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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