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Review

Fundamentals of bone vasculature: Specialization, interactions and functions

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ABSTRACT

Angiogenesis, hematopoiesis and osteogenesis are fundamental processes mediating complex and essential biological functions. In the bone marrow, endothelial cells (ECs) are a principal mediator of regulatory signals that govern hematopoietic and mesenchymal stem cells. EC and osteoblast interactions and niche functions of ECs are fundamental in maintaining bone health and coordinating repair and regeneration following injury. These cellular interactions are subject to dysregulation and deterioration under stress, aging, chronic disease states and malignancy. Thus, the prospect of manipulating the bone vasculature has tremendous potential to advance therapeutic interventions for the management of bone diseases. This review discusses the current state of vascular-skeletal tissue interactions focusing on osteoblast and hematopoietic stem cells interaction with ECs.

1. Introduction

The bone marrow (BM) is an essential tissue comprised of an intricate vascular network and a rich plethora of cell types responsible for supporting fundamental processes such as hematopoiesis and osteogenesis [1,2]. Hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), occupy specialized microenvironments known as niches. Each niche is comprised of a range of cell types, including endothelial, osteoprogenitor, mesenchymal, perivascular, stromal and even neuronal cells [3]. During homeostasis, the HSC niche maintains a strict balance between quiescent, differentiated and proliferative states that aid in replenishing the erythroid-, myeloid- and lymphoid- cell lineages but without exhausting the HSC pool [4].

The bone vasculature plays a fundamental role in orchestrating osteogenesis and hematopoiesis through the generation of various angiocrine factors. Here, capillaries dominate crosstalk interactions with resident cells such as HSCs and osteoprogenitors. Furthermore, different regions of the vasculature, defined as type-L or type-H endothelium, are associated with specific vascular niches [5] (Fig. 1). Type-H vessels are fed by arterioles and hence have higher blood flow and higher levels of oxygen and nutrients as compared to type-L vessels [6,7]. Type-H capillaries are typically localized in close proximity to runt-related transcription factor 2 (Runx2)- and osterix-expressing osteoprogenitors at the site of active bone growth in the metaphysis and in the periosteum and endosteum of the diaphysis regions of bone, where they can be identified by their high expression of endomucin (Emcn) and cluster of differentiation 31 (CD31) [5,8]. Type-L endothelial cells (ECs), however, exhibit lower expression of Emcn and CD31, but are also characterized as Sca-1low and VEGFR3+ [9–11] and consist predominantly of sinusoidal-like vessels [12]. The identification of EC subtypes within the bone vasculature has provided greater understanding of the heterogeneity of ECs and to what extent they may have a role in mediating bone function in health and disease. More specifically, recent investigations into the crosstalk between ECs, particularly type-H ECs, and progenitor cells such as HSCs [13,14] and osteoprogenitors [8] has been a source of keen interest whereby angiocrine crosstalk between these cell types plays a key role in mediating bone haemostasis and of particular interest, in the development of specific conditions. The bone niches, undergoes dramatic changes during conditions such as aging, infection, development of primary hematological and osteoblastic cancers [11,15] or secondary tumours [16,17] and bone damage (e.g. fracture, radiation and non-hematological diseases (NHDs)). The role of the endothelium on cellular processes in health and disease has been the source of multiple reviews [2,11,18,19]. This review aims to focus specifically on the interactions between ECs and osteoblasts and ECs and HSCs during homeostasis, aging and various pathological diseases.

1.1. Angiogenesis in other models versus bone angiogenesis

Angiogenesis is a vital process that ensures efficient neosynthesis of

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blood vessels and plays a fundamental role in an array of physiological processes, including embryogenesis, homeostasis and wound healing [20,21]. However, this process can become dysregulated during various pathological conditions such as cancer metastasis, neurological disorders (e.g. Alzheimer's disease, AD), liver diseases (e.g. fibrosis) and lung disorders (e.g. chronic obstructive pulmonary disease, COPD) [21,22]. Angiogenesis is initiated in response to tissue hypoxia, which leads to elevated expression of EC-derived hypoxia-inducible factor 1-α (HIF-1α). This, in turn, induces the upregulation of other proangiogenic factors such as fibroblast growth factors (FGFs) [23], epidermal growth factors (EGFs) [24], transforming growth factor-β (TGF-β) [25] and vascular endothelial growth factor (VEGF) [20,26]. In addition, proteases are released and promote proteolytic degradation and remodelling of the extracellular matrix (ECM). The result is vessel vasodilation in the affected area, degradation of the basement membrane and detachment of pericytes, EC migration and enhanced vascular permeability [27].

In this section, we will discuss typical angiogenesis and highlight key specific differences to angiogenesis in bone tissue. Angiogenesis occurs in three forms: intussusceptive, sprouting and the bone-specific mode known as, bulging. The intussusceptive model is characterized by the splitting of an existing blood vessel and occurs during the formation of lung and heart tissue [28,29]. Sprouting, the most commonly observed mode, is characterized by the formation of a "tip cell", a type of specialized EC which guides the direction of blood vessel development [30,31]. Here, tip cells extend their filopodia into the surrounding tissue and migrate along a VEGF, EGF and FGF concentration gradient leading to the formation of a stalk elongation [29,32] (Fig. 2). During certain conditions such as tissue ischemia, diabetic retinopathy and cancer development, endothelial progenitor cells (EPCs) are recruited to the angiogenic site where they differentiate into highly proliferative EC stalk cells that go on to comprise the majority of the newly developed blood vessel in a process known as vasculogenesis [33,34]. ECs recruit pericytes to the newly synthesized branches by the release of platelet-derived growth factor-BB (PDGF-BB) [35]. This essential process enables the maturation and stabilization of blood vessels and prevents excessive sprouting [36]. Simultaneously, the size of new blood vessels is controlled by a negative feedback loop involving VEGF-induced secretion of the notch-1 receptor ligand, delta-like 4 (DLL4). Enhanced expression of DLL4 by tip cells then acts on notch expressed by stalk cells which in turn downregulates the expression of VEGFR2 and thus EC proliferation. Downregulation of VEGFR2 leads to a lowering in the responsiveness of stalk ECs to VEGF and thus ensures the tip cell remains in the lead of the branch. Finally, following anastomoses of two opposing tip cell led branches, blood flow is restored, and ECs become quiescent [20,29].

While most tissue vessels undergo intussusceptive or sprouting modes of angiogenesis, certain tissues such as the bone exhibit vessel bulging angiogenesis, a mode involving endothelial structures known as "bulges" or "buds" that form between two columnar vessels [37]. These structures, which stem from type-H capillaries in the metaphyseal region, are comprised of multi-endothelial layers, which are notably devoid of tip cells, but yet still project filopodia like structures into the surrounding chondrocyte matrix and follow an angiogenic VEGF concentration gradient (see Fig. 1) [37–39]. Anastomoses between two neighbouring vessels is achieved when two bulges merge to form an

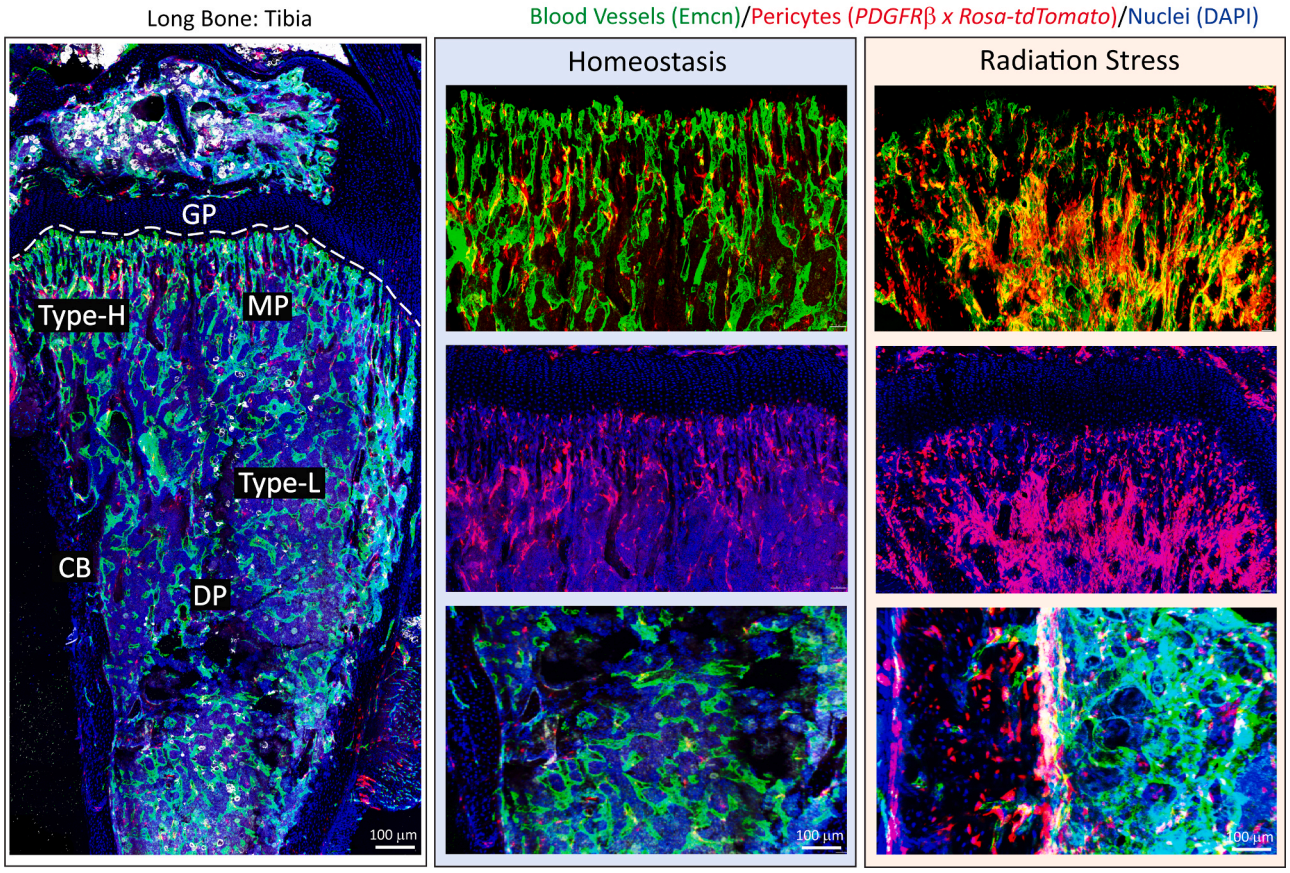

Fig. 1. 3D imaging of blood vessels and perivascular cells in homeostasis and radiation stress. Blood vessels in the mouse tibia bone are labelled in green using a fluorescently labelled anti-Emcn Ab, pericytes are visualized in red through the use of a genetic mouse model, PDGFRβ x Rosa-tdTomato and DAPI is used to stain the nuclei of all nucleated cells (centre & right). These panels highlight changes in the bone microenvironment under homeostasis (centre) and radiation induced stress (right). Under radiation stress induced conditions, the blood vessels become more dilated and pericyte numbers are increased as they undergo expansion. GP, growth plate; MP, metaphyseal; CB, condensed bone; DP, diaphyseal; Emcn, endomucin; PDGFRβ, platelet derived growth factor beta.

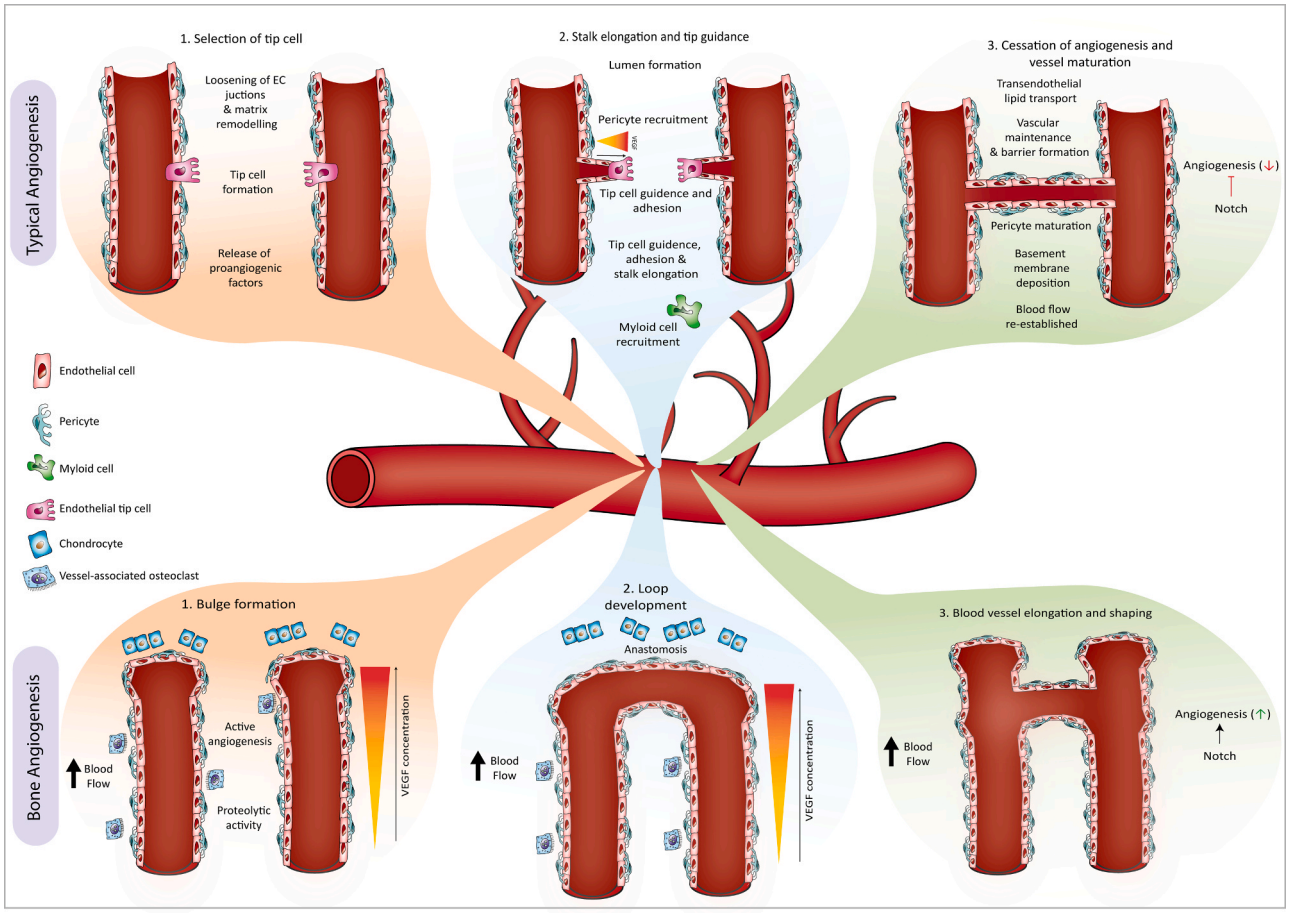

Fig. 2. Angiogenesis. Angiogenesis in the retina and bone. Angiogenesis plays a vital role during foetal development and in maintaining the microvasculature. Fundamentally, traditional angiogenesis requires the formation of a tip cell, followed by stalk elongation which extend in the direction of higher VEGF concentration. More specifically, selection of a tip cell requires loosening of EC junctions and matrix remodelling (VE-cadherin, MMPs), tip cell formation (VEGFR2, DLL4, Jag-1, NRP-1, HIF-1α, MT1-MMP, PGC-1α) and the release of proangiogenic factors (VEGF, FGFs, Ang-2, various chemokines). Next, stalk elongation requires lumen formation (VE-cadherin, CD34, sialomucins, VEGF), pericyte recruitment (PDGFs, Ang-1, notch, ephrin-B2, FGF), tip cell guidance and adhesion (semaphorins, ephrins, integrins), tip cell guidance, adhesion and stalk elongation (semaphorins, ephrins, VEGFR1, notch, NRARP, FGFs, EGFL7) and myeloid cell recruitment (Ang-2, SDF-1α, PIGF). Lastly, cessation of angiogenesis and vessel maturation requires transendothelial lipid transport (VEGF), vascular maintenance and barrier formation (VEGF, Ang-1, FGFs, notch, VE-cadherin), pericyte maturation (PDGF-β, ephrin-B2, Ang-1, notch, TGF-β1), basement membrane deposition (TIMPs, PAI-1) and re-establishment of blood flow. Distinctly, in the bone tissue, a unique form of angiogenesis has been observed, defined as vessel bulging. In this subtype of angiogenesis, the signalling molecule, notch, has been shown to act opposingly to its function in other tissues, and instead supports EC proliferation and vessel growth. Furthermore, chondrocytes support new blood vessel growth via the secretion of various angiocrine factors (FGFs, VEGF). Type-H vessel formation, presumably through building, is aided by the release of PDGF-BB from preosteoclasts. VE-cadherin, vascular endothelial cadherin; MMP, matrix metalloproteinase; VEGFR, vascular endothelial growth factor receptor; DLL4, delta-like 4; Jag-1, jagged-1; NRP-1, neuropillin-1; HIF-1α, hypoxia inducible factor-1α; MT1-MMP, membrane-type-1 matrix metalloproteinase; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator; FGF, fibroblast growth factor; Ang, angiopoietin; CD34, cluster of differentiation 34; PDGF-B, platelet derived growth factor Subunit B; NRARP, notch regulated ankyrin repeat protein; EGFL7, epidermal growth factor-like domain 7; SDF-1α, stromal cell derived factor-1 alpha; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TIMP, TIMP metallopeptidase inhibitor 1; PAI-1, plasminogen activator inhibitor-1.

arch/loop. Interestingly, bulge and arch structures are observed in proximity to hypertrophic chondrocytes, a known source of pro-angiogenic factors e.g. FGFs and VEGF, localized at the growth plate [40]. In mice, while arch structures remain prevalent into adulthood, the formation of bulge structures notably declines, which is consistent with a reduction in type-H vasculature. Distinctly in bone angiogenesis, the signalling molecule, notch, supports proliferation and vessel growth, in contrast to its established antiangiogenic function in the endothelium of other tissues [5,39,41] (Fig. 1). Additionally, PDGF-BB supports bone angiogenesis of type-H endothelium during bone remodelling following its release by preosteoclasts and subsequent recruitment of EPCs and MSCs [42,43]. However, whether PDGF-BB directly regulates angiogenesis as with non-bone vessel growth remains unknown, as does the angiogenic mode by which these vessels are developed. Overall, the signalling factors that govern the prevalence of bulging vs. other forms of angiogenesis is poorly understood and requires further investigation.

Microvascular angiogenesis is also mechanically regulated by the flow of luminal and abluminal fluids, which can be perturbed by tissue compression [44,45]. Compression of the bone tissue during the vessel sprouting and branching phase of angiogenesis inhibits neovascularization, while compression during the elongation phase promotes it [46]. These effects are regulated by the yes-associated protein (YAP)/ transcriptional co-activator with PDZ-binding motif (TAZ) mechanotransduction pathway, which controls the stiffness and adhesiveness of the ECM [47]. A critical mediator of this pathway is piezo1, a mechanosensitive cation channel known to be critical in bone formation [48,49]. Impairment of piezo1 leads to reduced notch signalling and deranged bone formation [50]. Recent investigations have further

shown that these changes coincide with the downregulation of phosphorylated phosphoinositide 3-kinases (PI3K) – protein kinase B (Akt), CD31 signalling and calcium-activated proteolytic calpain activity during bone angiogenesis [50]. These studies highlight the fundamentals of both generic and bone-specific vessel formation. Advances in these areas may aid in furthering our understanding and preventing dysregulated angiogenesis in disease states.

1.2. Angiocrine signalling effecting the role of EC-osteoblast function in health and disease

1.2.1. Early development and homeostasis

The role of ECs and osteoblasts in bone development can be traced to the later stages of embryogenesis following the formation of mesenchymal condensates [32,37,51]. During development, angiogenesis and the differentiation of MSCs into chondrocytes and osteoblasts are regulated by expression of HIF-1α and subsequent expression of VEGF [52]. Briefly, during the early stages of bone tissue, chondrocytes migrate to primary ossification centres (POCs) where they rapidly proliferate and become hypertrophic. These cells secrete pro-angiogenic factors such as VEGF [53–55] and FGFs [56] to promote vascular invasion of developing bone tissue. At sites of bone growth, type-H vessels provide nutritional resources to osterix^{+} osteoprogenitors and secrete PDGFs, noggin, FGFs and TGFs to aid in the maintenance and self-renewal of the osteoprogenitor population [5,51]. Osteoprogenitor cells, in turn, regulate the phenotype of blood vessels [57] via the expression of SLIT homolog protein 3 (SLIT3) [58] and VEGF [51,59]. These processes also occur at sites of bone growth and renewal in young and adult tissue.[51] In all instances, notch signalling is an important mediator of both type-H capillary angiogenesis and osteogenesis in the bone [39]. Activation of the notch receptor requires cleavage by proteolytic enzymes following ligation with its respective ligands (e.g. a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10)). Both loss-of-function mutant models of notch and ADAM10 in ECs had poor growth of the bone tissue and plate size [60]. In addition, notch positively regulates the expression of the bone morphogenic protein (BMP) antagonist, noggin, which controls the size of the bone plate [1,39,61] (Fig. 3, central panel). Moreover, ECs are known to

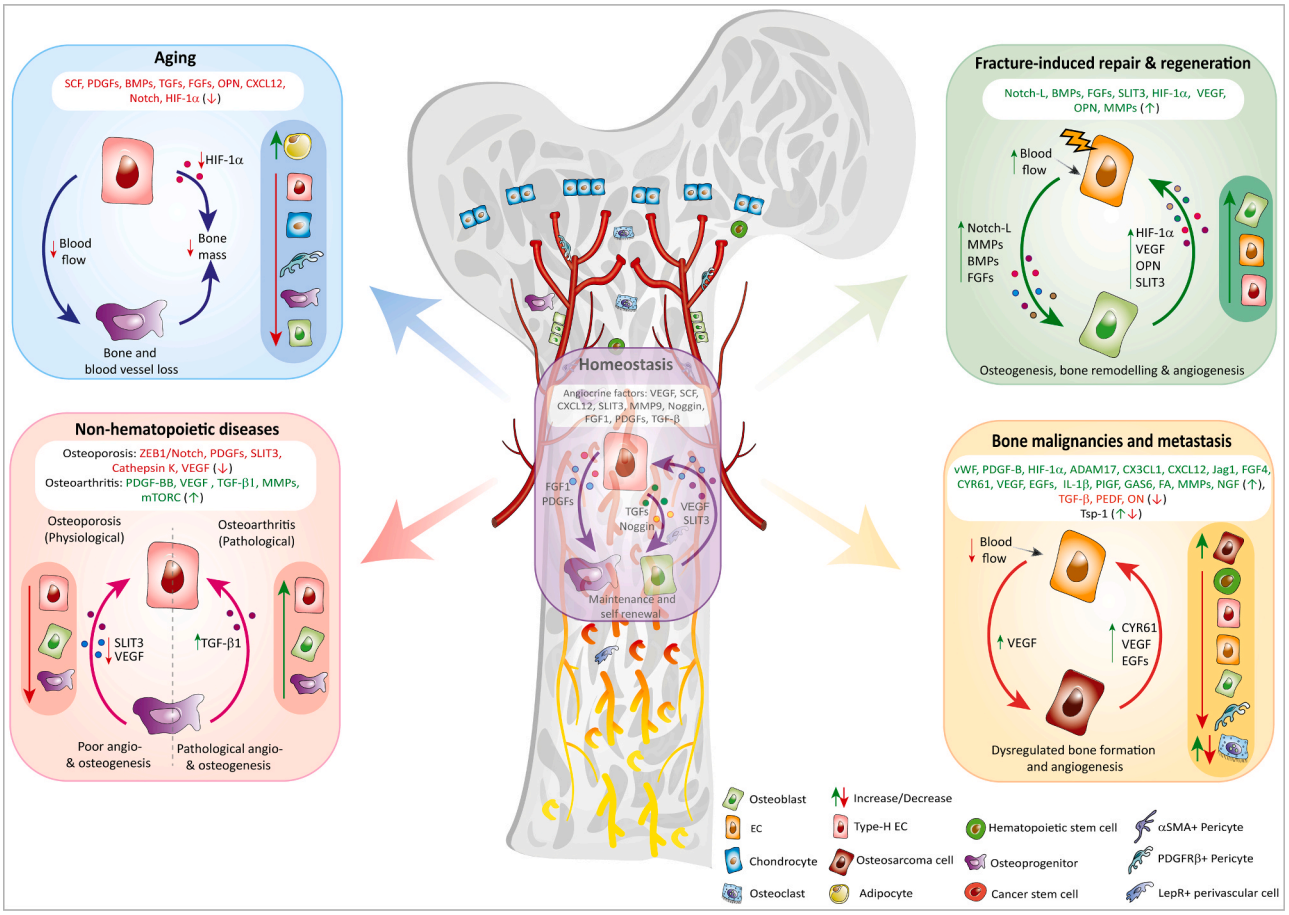

Fig. 3. EC-Osteoblast interactions in bone. Angiocrine signalling between ECs and osteoprogenitors/osteoblasts in the bone microvascular environment. Angiocrine signalling between these cell types plays a vital role in supporting the bone vascular environment during various conditions. During homeostatic conditions, release of EC-osteoprogenitor cell angiocrine factors supports maintenance and self-renewal of the bone vascular niche. However, aging has been associated with a loss of type-H ECs which subsequently leads to bone loss and poor fracture healing. Bone repair is a vital process, which is supported via the generation of several key angiogenic factors to support revascularisation and osteogenesis. Cancer cells are also able to take advantage of the bone microenvironment where they lead to dysregulated angiogenesis and bone loss. Lastly, NHDs such as osteoarthritis and osteoporosis support pathological and physiological angio- and osteogenesis, respectively. EC, endothelial cell; HSC, hematopoietic stem cell; SCF, stem cell factor; PDGF, platelet-derived growth factor; BMP, bone morphogenetic protein; TGF, transforming growth factor; FGF, fibroblast growth factor; OPN, osteopontin; HIF-1α, hypoxia inducible factor 1α; CXCL12, C-X-C motif chemokine 12; PDGF-BB, platelet-derived growth factor BB; VEGF, vascular endothelial growth factor; mTORC, mammalian target of ramamycin complex; ZEB1, zinc finger E-box-binding homeobox 1; SLIT3, SLIT homolog protein 3; MMP, matrix metallopeptidases; Tsp-1, thrombospondin-1; vWF, von Willebrand factor; ADAM17, A disintegrin and metalloprotease 17; CX3CL1, C-X3-C motif chemokine ligand 1; Jag-1, jagged 1; EGFL7, epidermal growth factor like domain 7; IL-1β, interleukin-1β; PIGF, placental growth factor; GAS6; growth arrest-specific gene-6; NGF, nerve growth factor; PEDF, pigment epithelium-derived factor; αSMA, alpha-smooth muscle actin; LepR, leptin receptor; notch-L, notch ligand; CYR61, Cysteine-rich angiogenic inducer 61; FA, fatty acids; ON, osteonectin.

contribute towards vessel and bone formation via zinc-finger E-box--binding homeobox 1 (ZEB1), an essential mediator of notch signalling. Here, an EC-specific ZEB1 deletion simultaneously impeded bone and type-H vessel formation. However, administration of liposome-packaged *Zeb1* genes was found to promote angiogenesis-dependent osteogenesis via recovery of the notch signalling pathway [62]. Osteoblasts also regulate angiogenesis and osteogenesis through schnurri3 (SHN3), a zinc finger protein critical in postnatal bone formation and generation of blood vessels via the SLIT3/robo1 complex [58]. Of particular interest, in *Shn3*$^{-/-}$ mice, an enhanced prevalence in type-H ECs occurs prior to the increase in bone formation, highlighting the fundamental role that EC angiocrine signals play in driving osteogenesis (Fig. 3, bottom-left panel).

1.2.2. Aging and age-related diseases

Healthy remodelling of the skeletal system requires a continuous cycle of balanced bone construction and resorption. In aged individuals, however, the rate of bone resorption exceeds that of formation resulting in loss of bone mass and increased risk of fracture [63]. In addition, during biological aging, the type-H endothelium gradually declines, causing a reduction in blood flow and the expression of the aforementioned angiocrine factors, particularly HIF-1α [30]. This is generally associated with poor angiogenesis and bone formation [40], implying that changes in blood flow may be caused by age-related bone loss (Fig. 3, top-left panel).

Similar observations are found in mice exhibiting an osteoblast-specific deletion of HIF-1α [64]. Furthermore, aged mice exhibiting an EC-specific deletion of the E3 ubiquitin ligase, Von Hippel-Lindau (VHL) ligase, or administration of the iron chelator deferoxamine mesylate all result in stabilization of HIF-1α and enhance type-H blood vessel generation and osteogenesis [5,64,65]. Similar conditions can occur in an age-independent manner following myocardial infarction where the loss of the type-H endothelium was shown to be dependent on the release of the proinflammatory cytokine, interleukin-1β (IL-1β) [66]. Stroke is also associated with bone loss and dysfunction. Recently, investigations into the effect of stroke and exercise on osteovascular function in vivo determined that stroke reduced the vessel density in close proximity to the bone [67]. Interestingly, moderate aerobic exercise during recovery was associated with a loss of type-H endothelium and, as such, was suggested to be detrimental to bone remodelling during early stroke recovery.

1.2.3. Fracture induced repair and regeneration

The significance of blood vessels in the healing of bone defects has been widely recognized [32,40,68], and unlike many other organs, bone tissue has a high regenerative potential. Following damage (e.g. bone fracture), the injured site becomes encapsulated by inflammatory exudate and a hematoma forms [69]. The local microenvironment at the fracture site exists in a hypoxic environment and thus results in enhanced expression of HIF-1α and VEGF [70,71]. In addition, this ongoing hypoxic environment leads to elevated expression of the osteogenic factor, BMP2 by ECs [72]. Subsequently, the fractured site is invaded by newly synthesized vasculature that supplies blood flow to the re-establish local environment and acts as a template for osteoclast-fibrocartilaginous callus formation, where osteoblast precursors are recruited [55,73,74]. Here, the platelet derived growth factor β (PDGFRβ) - PDGF-BB axis of osteoprogenitor cells has been shown to be critical in maintaining a proliferative, immature and migratory cell pool [75]. This is also controlled downstream by the induction of MMP9 and vascular cell adhesion molecule-1 (VCAM-1) signalling. Subsequently, the soft callus undergoes a VEGF-dependent calcification to form hardened new bone tissue [70,76]. VEGF also promotes the release of the proangiogenic protein, osteopontin and MMPs to induce remodelling of the ECM. *Opn*$^{-/-}$ mice exhibited a delay in the early vascularisation response and altered matrix remodelling and *mmp9*$^{-/-}$ or *mmp13*$^{-/-}$ mice exhibit poor cartilage remodelling, vascularisation and bone formation, a response which was rescued following administration of recombinant VEGF [74,77–79]. Furthermore, SLIT3 plays an essential role in angiogenesis and repair by promoting EC proliferation, migration and vessel growth both *ex vivo* and in vivo [59]. Its role in coupling angiogenesis and osteogenesis has been demonstrated through the use of SLIT3 mutant mice, which have poor type-H vessel formation and bone regeneration responses. At the same time, overexpression led to improved callus formation and hematopoiesis during bone repair [58] (Fig. 3, top-right panel). These findings also reinforce the notion that interactions between the type-H endothelium and osteoblasts are critical in bone repair and regeneration.

1.2.4. Non-hematopoietic diseases on the bone

Endothelial and osteoblast interactions play crucial roles in the pathology of various NHDs. For example, chronic inflammatory diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA) are associated with inflammation of the joints, degradation of the bone and cartilage [80], the development of joint deformities [81] and increased articular angiogenesis [82]. Both RA and OA patients exhibit chronically elevated levels of the proinflammatory cytokines IL-6, IL-11 and tumour necrosis factor (TNF) in their synovial fluid, the synovium and the articular cartilage [83,84]. These factors can lead to impaired osteoblast-dependent bone repair and even bone loss if the inflammation remains uncontrolled [80]. In patients suffering from OA, TGF-β1 is expressed at higher levels and is associated with an enhanced recruitment of MSCs and type-H ECs, suggesting angiogenic and osteogenic coupling in these diseases [85]. Indeed, OA can be induced in mice by overexpression of TGF-β1, to which osteoblasts are a major source [86] (see Fig. 3, bottom-left panel).

EC and osteoblast crosstalk also play a fundamental role in other conditions such as osteoporosis. Patients with this metabolic condition exhibit greater rates of osteoclast-dependent bone resorption as compared with osteoblast-dependent bone formation, resulting in reduced bone mass and density [63]. Furthermore, mouse models of senile, postmenopausal and glucocorticoid-induced osteoporosis have reduced numbers of type-H ECs [42,43,87], and of interest, aged individuals also have reduced numbers of type-H cells, which is consistent with their greater risk of developing osteoporosis [88]. Indeed, potential therapeutic efforts involving inhibition of osteoclast action resulted in an enhanced prevalence of type-H endothelium and maintenance of osteoblast numbers, demonstrating their importance towards healthy osteogenesis [89]. These effects were hypothesized to be, in part, due to the survival-promoting effects of VEGF upregulation by type-H ECs. Osteoporosis has also been linked to downregulation of the osteoblast proangiogenic factor, SLIT3, which again coincided with a loss of type-H ECs, that was restored in a murine model of postmenopausal osteoporosis following treatment with exogenous SLIT3 [58] (Fig. 3, bottom-left panel). In glucocorticoid-induced osteoporosis, the reduction in type-H endothelium was associated with inhibition of PDGF-BB from pre-osteoclasts [89]. Interestingly, osteoporosis in humans has also been linked to reduced expression of ZEB1 and a consequential disruption of notch signalling. In a model of ovariectomy-induced (postmenopausal) osteoporotic mice, an administration of liposome delivered *Zeb1* gene (described in section 3.1.1.) resulted in a partial reversion of the osteoporosis, characterised by restoration in the number of Runx2^{+} and osterix^{+} osteoprogenitors and restored bone function.[62].

Overall, greater emphasis should be placed on the balancing of the growth of type-H endothelium in these disease states, and an approach developed to promote the regeneration of type-H endothelium in patients with osteoporosis or inhibit angiogenesis of type-H blood vessels in OA patients could be a novel therapeutic approach. Moreover, the role of the bone vascular subtypes in the pathogenesis of conditions such as osteogenesis imperfecta and disuse osteoporosis remains an intriguing, yet to our knowledge an unexplored topic, as these diseases are associated with impaired osteoblast function or compromised ECM.

1.2.5. Bone malignancies and metastasis

The bone is uniquely susceptible to the development of hematologic cancers, primary tumours (osteosarcoma, chondrosarcoma and Ewing's sarcoma) and secondary tumours following the arrival of disseminated tumour cell (DTCs) [90]. Cancer cells predominantly reside within the endosteal BM vascular niche, where their growth is facilitated by interactions with resident tissue cells such as ECs, osteoblasts, osteoclasts and HSCs [91]. Consequently, tumours are often accompanied by the formation of osteolytic or osteoblastic lesions and the impairment of hematopoiesis [92].

Bone tumours occupy an acidic and hypoxic matrix leading to the upregulation of HIF-1α, and in turn, VEGF [32,93]. Specifically, osteosarcoma cells, which are of osteoblastic lineage, support angiogenesis through the expression of the ECM protein, cysteine-rich angiogenic inducer 61 (CYR61); a factor associated with the upregulation of the proangiogenic factors VEGF, CD31 and angiopoietins and downregulation of the antiangiogenic factors, thrombospondin-1 (Tsp-1) and osteonectin [94,95]. Together, these factors lead to increased intratumoral vascularisation and vessel diameter, whereby the latter confers reduced blood flow, which of interest has been shown to facilitate resistance to chemotherapy [68]. Recently, upregulation of miRNA-150–5p activity, which inhibits VEGF-A activity, was found to reduce the proliferation and invasiveness of osteosarcoma [96]. Cancer stem cells (CSCs) in the bone are known to secrete a variety of osteoblast-stimulating factors such as BMPs, EGFs, PDGFs and endothelin-1 (ET-1), which downregulate the protein Dickkopf-related protein 1 (DKK-1) and increases osteoblastogenesis [97,98]. Remarkably, osteoblastic lesions are now known to arise directly from ECs. Here, prostate-derived cancer cells that disseminate to the BM release BMP4, which induces tumour-associated ECs to differentiate into osteoblasts [99] (Fig. 3, bottom-right panel). By comparison, DTCs in the bone originating from the lung renal, breast and to a lesser extent, thyroid are often associated with the formation of osteolytic lesions associated with enhanced levels of the osteoclast stimulating factor, receptor activator for NFκB ligand (RANKL), secreted by osteoblasts [100–103]. Combined with a gradual loss of osteoblasts in an increasingly apoptotic environment leads to bone loss over time. Overall, interactions between the endothelium and bone-forming cells are underappreciated, particularly during the development of primary bone tumours that involve the dysregulated activity of osteoblasts, mandating further study. Moreover, more work is needed to determine the relationship between ECs and osteoblasts in the context of cancer metastasis, since highly vascularised tumours can result in osteoblastic and osteolytic lesions.

1.3. Angiocrine signalling effecting the role of EC - HSC function in health and disease

1.3.1. Early development and homeostasis

HSCs play a fundamental role in maintaining homeostasis in the bone microvasculature [104,105]. Interestingly, during mouse embryogenesis, the first HSCs are not detectable until embryonic day 10.5, the so called "third wave" of hematopoiesis, where they derive directly from hemogenic ECs [106,107]. Before localising to the spleen and BM in later development, HSCs can be found in the fetal liver and umbilical cord where the local endothelium is known to aid in their proliferation and differentiation [108]. The study of EC – HSC interactions during this early stage is fundamentally limited by difficulties in reproducing the HSC fetal niche with *ex vivo* or in vitro techniques. Hence our understanding of the driving factors remains primitive. In zebrafish models, live imaging has revealed that the HSCs associated with mesenchymal stromal cells become surrounded by ECs that support their development [109]. In late fetal development and during the first 3 weeks of life, HSC proliferation in the BM increases whereby the HSCs adopt a more quiescent phenotype [110]. Following this, fetal HSCs become phenotypically indistinguishable from adult HSCs.

In adults, the precise localization of HSCs within the BM vascular niche remains a topic of controversy but are typically reported to be localized within distinct BM vascular niches. For example, both dividing (long term, LT-) and non-dividing (short term, ST-) HSCs [111] have been observed within the diaphyseal bone region, in close proximity to sinusoidal blood vessels [112]. Here, quiescent HSCs are found proximal to NG2 + -pericytes, which surround endosteal arterial vessels [113]. As they migrate towards LepR+-perisinusoidal vascular niches, HSCs adopt a more proliferative phenotype [10,114]. LT-HSCs have been reported to be localized within the endosteum region, in close proximity to sinusoidal vessels where they exhibited limited motility [115]. Elsewhere, studies have reported that the majority of HSCs are located in the perivascular space in proximity to stem cell factor (SCF)-expressing stromal cells, where they exhibit high motility [116]. Recently, the notion of HSCs preferentially co-locating with particular cell types has been challenged, with suggestions that apparent co-localization is an artefact of HSC and niche abundance [18]. These variations highlight a need for further investigation and understanding of the complexities of HSCs pervasion within the BM.

Angiocrine crosstalk between ECs and HSCs is essential in regulating whether HSCs are in a quiescent, proliferative or differentiating state [1,117]. Under homeostatic conditions, type-H and type-L ECs are the main source of SCF [118] and C-X-C motif chemokine 12 (CXCL12) [119], respectively, which aid in the maintenance, retention and self-renewal of HSCs (Fig. 4, top-left panel) [120]. ECs also up-regulate the notch ligand, jagged-1 (Jag-1), which aids in the maintenance of the HSC pool [117,121,122]. Furthermore, evidence from zebrafish models suggests that ECs can also modulate HSC expansion through the transcription factor, Krueppel-like factor 6 (KLF6), which in turn, controls the expression of the chemokine (C-C motif) ligand 25b (CCL25b) (Fig. 4, top-left panel) [123]. Recently, ECs have also been demonstrated to modulate the proliferation and egress of HSCs via downstream effects of the EC-derived transcription factor inhibitor proteins, DNA-binding protein inhibitor 1 and 3 (ID1 and ID3) [124]. Although the precise mechanism of ID's remains elusive, it is thought they are responsible for controlling the expression of VEGFR2. Loss-of-function ID1 and ID3 ECs exhibited disrupted type-L endothelium, enhanced HSC proliferation, differentiation, migration and exhaustion [124] (Fig. 4, top-left panel).

1.3.2. Aging and inflammation

In aged individuals, the bone microvasculature becomes augmented and physiological processes are consequently disrupted. With age comes a reduction of the type-H endothelium and a concomitant reduction in the number of pericytes which are responsible for promoting HSC quiescence in the BM [68]. Aged BM ECs express significantly lower levels of SCF, CXCL12, and notch ligands [5,13,19,125] which subsequently results in increased HSC proliferation and a loss of quiescence [30], hence aged individual tend to exhibit higher numbers of HSCs, but fewer that are functional and regenerative (Fig. 4, top-right panel). These effects were found to be coeval with up-regulation of several cytokines [126,127] associated with cellular proliferation and inflammation, in particular the interleukins, IL-1β and IL-6 (Fig. 4, top-right panel). Of interest, these mechanisms also facilitate the expansion of CSCs in the BM [68].

Inflammation is a critical protective immune response initiated via the generation of various danger associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs) released following tissue damage or infection, respectively [128]. During inflammation, BM ECs recognize these molecules via their cell surface pattern recognition receptors (PRRs), leading to activation of various complex signalling pathways and secretion of various proinflammatory cytokines such as interleukins, TNF and interferon-α (IFN-α) [129]. Moreover, ECs also up-regulate granulocyte-colony stimulation factor (G-CSF) and granulocyte macrophage-colony stimulation factor (GM-CSF), which induce HSC proliferation, migration and differentiation [130]. These responses are typical of bacteremia following a serious Escherichia coli

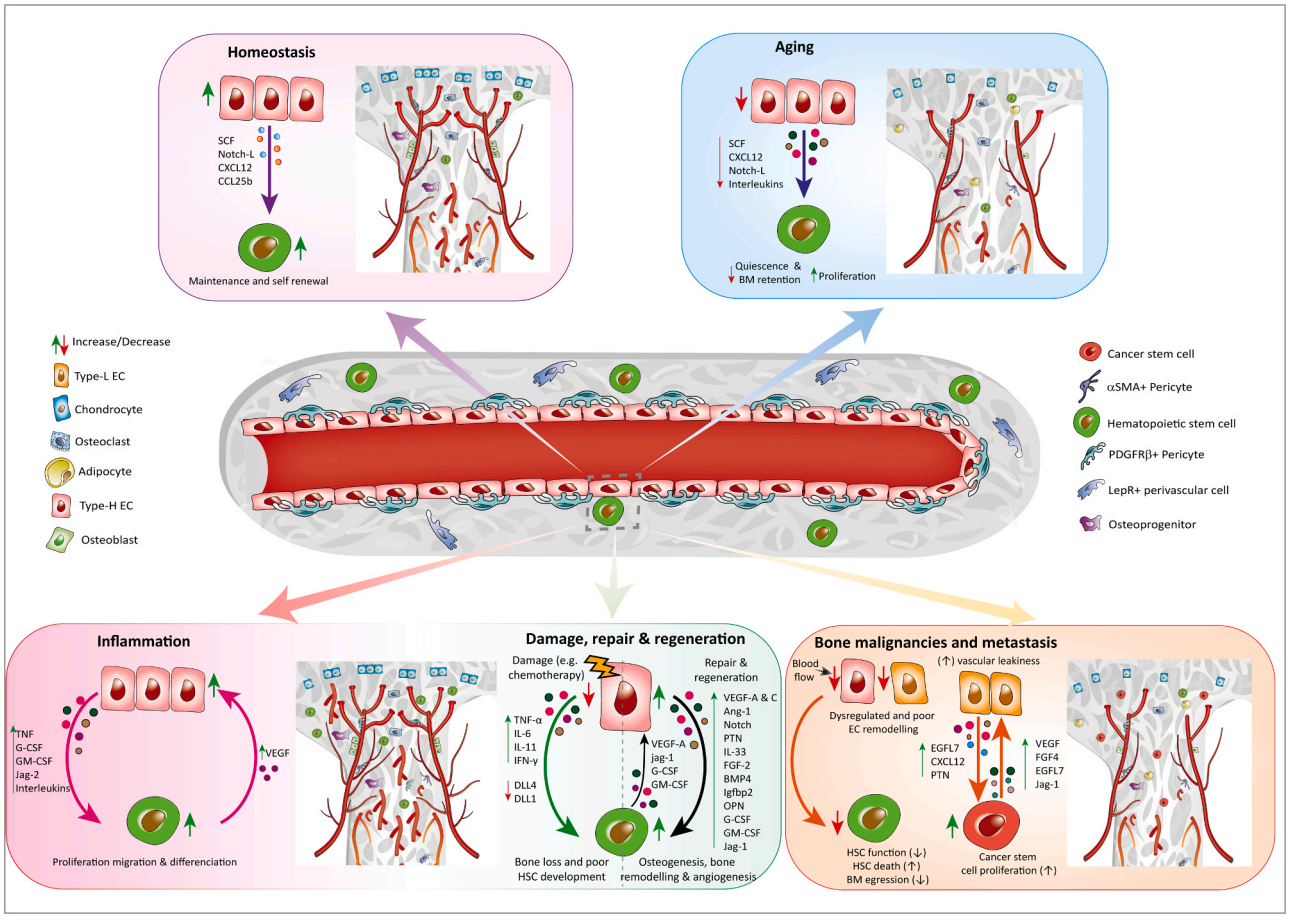

Fig. 4. EC-HSC crosstalk in the bone marrow microenvironment. Angiocrine signalling between ECs and HSCs in the bone microvascular environment. Angiocrine signalling supports the bone vascular microenvironment under various states and conditions. Under homeostatic conditions, signalling between ECs and HSCs supports HSC maintenance and self-renewal. However, during aging there is a loss of H-type ECs and their corresponding angiogenic factors, thus supporting HSC quiescence. During inflammation EC-HSC interactions support proliferation and migration of ECs and HSCs, respectively. Under conditions of bone malignancies, cancer stem cells dominate over healthy HSCs, a response supported by changes in angiocrine factors generated by the ECs and HSCs. Lastly, damage to the bone vasculature can lead to the release of many damage-associated and pro-inflammatory factors leading to bone loss and poor healing such as that induced following chemotherapy. Efficient healing of the bone microenvironment is pivotal to maintain bone function. EC-HSC generated angiocrine factor aid in this response, supporting osteogenesis, bone remodelling and angiogenesis. SCF, stem cell factor; CXCL12, C-X-C motif chemokine 12; TNF, tumour necrosis factor; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; Jag-2, jagged-2; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; IL-1β, interleukin-1β; IFN-γ, interferon-gamma; DLL, delta-like; Ang, angiopoietin; BMP, bone morphogenetic protein; Igfbp2, insulin-like growth factor-binding protein; OPN, osteopontin; IL-33, interleukin-33.

infection for example [131], where G-CSF and GM-CSF act in a paracrine and autocrine manner, whereby the latter generates a positive feedback loop to support further cytokine generation and amplify the inflammatory response [132,133]. Simultaneously, ECs down-regulate CXCL12 and SCF, which are vital for the maintenance of the HSC pool during both acute and chronic inflammatory responses [118,134,135]. For example, during diabetes mellitus, where patients are susceptible to the development of atherosclerotic plaques, HSC protecting factors, CXCL12, and Ang-1 are chronically down-regulated in BM ECs, due to disruption of EGF-receptor (EGFR) signalling [136]. Furthermore, in response to proinflammatory stimuli such as LPS and TNF, ECs up-regulate various cell activation markers, including Jag-2, which supports the proliferation of HSCs [137]. In addition, inflammation generates hypoxic regions within the BM, which leads to the up-regulation of VEGF/VEGFR2 by ECs/HSCs and thus enhanced angiogenesis [129,138] (Fig. 4, bottom-left panel).

Inflammatory and aging bone vascular niches share some similarities, including enhanced levels of proinflammatory cytokines, altered myeloid differentiation bias and an impaired HSC self-renewal capacity [133]. Of particular interest in aged individuals, enhanced levels of IL-1, IL-6 and TNF have been observed and may in part explain the enhanced rates of myelopoiesis and adipogenesis in the aged bone microenvironment [139,140] and the aptly named "inflammaging" defined by chronic age-associated inflammation [11,14,141] (Fig. 4, bottom-left panel).

1.3.3. Damage, repair and regeneration

Radiation is one of the most commonly used therapies against various hematological malignancies. Despite this, radiotherapy remains an aggressive option that can yield significant tissue damage, reduce hematopoietic populations and introduce mutations within the hematopoietic lineage [142,143]. Radiation is also associated with damage of the endothelium, whereby vessel vasodilation and permeability are induced, sinusoidal EC numbers are reduced, and changes in protein transcription are found. The bone is a highly regenerative environment whereby angiogenesis and osteogenesis aid in remodelling and repair of the bone microenvironment following damage [5,32,144,145]. Following radiation-induced myeloablation, ECs play a vital role in mediating repair and regeneration of the bone microenvironment [9]. Such effects are desired to support engraftment of donor HSCs that follow myeloablation. For example, sinusoidal ECs upregulate VEGF-A, VEGF-C [146], pleiotrophin [147], IL-33 [148] and FGF2 to support

regeneration of the HSC population [37] enabling the replenishment of the blood immune cell populations. HSC recovery has also shown dependencies on EC-derived Jag-1 [121,149], BMP4, insulin-like growth factor binding protein 2 (Igfbp2), Ang-1 and the protein kinase, Akt [149,150]. Indeed, transplantation of Akt-activated ECs or activation of Akt with mitogen-activated protein kinase (MAPK), induces regeneration and differentiation of HSCs [121]. Furthermore, apelin+ ECs, a subgroup of type-H ECs, expand following radiation therapy and have the potential to support arterial regeneration [151]. EC regeneration after myeloablation injury and thus maintenance and engraftment of HSCs is also dependent on the expression of EC-derived VEGFR2 in the BM vasculature [9] (Fig. 4, bottom-centre panel).

Chemotherapy is an alternative therapy option but has similar damaging consequences to the BM [143,152]. Interestingly, both treatments promote the expression of G-CSF and GM-CSF from ECs and HSCs, factors that encourage differentiation and lineage commitment of HSCs [152]. However, in direct contrast, the EC-derived notch ligands, DLL1 and DLL4, are downregulated following radio- or chemotherapy, despite mediating HSC to myeloid cell differentiation [153] (Fig. 4, bottom-centre panel). Even though substantial progress has been made in understanding how EC and HSC crosstalk contributes towards the repair and regeneration of the bone tissue, further investigations are required to fully elucidate this challenging topic. Doing so, however, is expected to lead to enhancement in the success and performance of donor BM grafts as treatment to various hematological cancers.

1.3.4. Bone malignancies and metastasis

Interactions between the ECs and HSCs during bone cancers is an area of growing interest since the bone vasculature can be indicative of hematological cancer prognosis. For instance, elevated levels of VEGF [154] and BM super-vascular formation are associated with a poor prognosis in acute myeloid leukaemia (AML) patients [155]. AML is characterized by disrupted BM vasculature with decreased vessel diameter, density, type-H endothelium in endosteum vascular niche, and increased density of microvessels, all amalgamating in impaired vessel perfusion [156,157]. Endothelial xenografts from human AML patients exhibited increased hypoxia around blood vessels, leading to increased endothelial ROS and nitric oxide levels, thus impairing HSC function and promoting cell death and outflow HSCs from the BM [157]. In the bone, vascular cells, osteocytes and tumour cells form part of a network that promotes tumour development and metastasis [32]. For example, EC-adhered lymphoma cells secrete FGF4 to activate EC FGF-receptor 1 (FGFR1), and up-regulate Jag-1, which in turn supports the proliferation of lymphoma cells [158]. Furthermore, CSCs also express high levels of epidermal growth factor-like 7 (EGFL7), a protein known to support angiogenesis and tumour growth [159]. The increased expression of E-selectin on bone ECs promotes bone metastasis by interacting with its ligand, golgi glycoprotein 1 (Glg1), on the surface of cancer cells [160,161] (Fig. 4, bottom-right panel).

Furthermore, in vitro studies have shown that AML cells located close to ECs possess resistance to chemotherapy [162,163]. More recently, in vivo studies have revealed that chemo- and radiation therapy expedite an increase in the type-H endothelium leading to expansion of pericytes and induction of CSC quiescence, rendering these cells resistant to therapy. Significantly, simulating an aged scenario by reducing the blood flow reverses these effects and increases CSC sensitivity to anti-cancer treatments [68]. Pharmacological inhibition of VEGFRs, PDGFRs and the proto-oncogene, tyrosine-protein kinase KIT (c-Kit) is also a known strategy to increase AML cell sensitivity to chemotherapy [164,165]. Indeed, inhibition of endothelial E-selectin improves the treatment of AML by extinguishing vascular niches that facilitate chemotherapy resistance [166]. The importance of the endothelium in the development of hematopoietic cancers such as myeloproliferative neoplasms in the HSC pool is also demonstrated by a predisposition to this condition in patients exhibiting an endothelial *JAK2V617F*-mutation, which enhances malignant hematopoietic regeneration following radiation injury [167]. JAK2V617F-bearing ECs up-regulate CXCL12, EGF and pleiotrophin following irradiation (Fig. 4, bottom-right panel). Recently, a subpopulation of sinusoidal apelin+-ECs was also found to aid in the maintenance and expansion of the HSC population following BM transplantation [151]. Since ECs comprise a critical regulator of bone cancers, it is not surprising that the level of EPCs can be related to patient prognosis. Patients with low levels of EPCs are typically more responsive to chemotherapy than those with high levels of EPCs [168]. Overall, there is clear potential in exploiting the function of ECs and HSCs or CSCs to improve the prognosis of cancer patients and the effectiveness of treatment regimes.

2. Conclusion

Our current understanding of the BM niche is rapidly advancing. Within just the last decade, there have been significant breakthroughs that have elucidated potentially critical and therapeutically relevant aspects of the BM vascular niche. Amongst the plethora of new information, perhaps some of the most relevant regards the interactions of specialized endothelial subtypes within the BM that exhibit specific functions and govern how HSC and osteoblasts respond to threatening conditions. However, there is much that is still poorly understood. In particular, we still lack a comprehensive model that describes the regulation of hematopoiesis and osteogenesis. Additionally, most of the data we have comes from murine models, and so findings may not directly translate to human scenarios. Nevertheless, furthering our knowledge in these areas will likely lead to revolutionary advancements in therapy for various diseases, including aging, infection, chronic NHDs and cancer.

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Conflicts of Interest

The authors have declared that no conflict of interest exists.

Author Information

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