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Skeletogenesis and the Hematopoietic Niche

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1. Introduction

The reciprocal regulation of the skeletal and the immune systems has been clinically appreciated for years. In particular, factors produced by immune cells during homeostasis and activation markedly affect the skeleton, which in turn affects the marrow niche environments (as reviewed in (Compston 2002)). This relationship also extends to an interdependence between bone and hematopoiesis during immune cell development, however the critical cell types and extracellular matrix components involved in establishing and maintaining hematopoietic niches within the bone marrow are only recently beginning to be defined. Indeed, some immuno-osseous disorders with hematopoietic defects such as bone marrow failure and immune dysfunction, as well as certain cancers, may result from a defective hematopoietic niche (Spranger et al. 1991; Kuijpers et al. 2004; Hermanns et al. 2005; Walkley et al. 2007; Walkley et al. 2007; Raaijmakers et al. 2010). Likewise during aging, a progressive decline in cell replacement and repair manifests in both the skeletal and hematopoietic systems with reduced bone mass and diminished blood cell formation respectively (as reviewed in (Rossi et al. 2008) and (Gruver et al. 2007)). Further, this altered hematopoiesis due to aging leads to deficient immune function and increased incidence of malignancies (Rossi et al. 2005; Janzen et al. 2006; Mayack et al. 2010). Thus, the dynamic relationship between skeletal and hematopoietic maintenance throughout life suggests that these clinical outcomes may ensue from cell signaling deficiencies or from defects in the structural environment supporting hematopoiesis. This chapter provides an overview of our current understanding of how hematopoietic niches may be established, how they promote hematopoiesis, and how the skeletal status may modulate niche function.

2. Coordinate skeletal and hematopoietic development

The vertebrate skeleton develops by one of two essential processes, endochondral (EO) and intramembranous (IO) ossification mechanisms (as reviewed in (Chan, D. and Jacenko 1998)). The direct differentiation of ectomesenchymal cells to osteoblasts in IO represents the rudimentary mechanism through which many skull bones and all periosteal bones form. The IO-derived bone is referred to as “dense”, “compact” or “cortical”, and as the names imply, is a solid bone with primary functions relating to weight bearing and protection (**Fig. 1C**). In contrast, EO relies on the generation of a cartilaginous skeletal blueprint that is gradually replaced by a “trabecular”, “spongy”, “cancellous” bone and a marrow capable of sustaining hematopoiesis (Chan, D. and Jacenko 1998; Mackie et al. 2008) (**Fig. 1C**). This replacement mechanism of EO is responsible for the formation of the vertebrate axial and appendicular skeleton, as well as certain cranial bones (Jacenko et al. 1991; Chan, D. and Jacenko 1998).

As EO initiates during embryogenesis, its distinctive feature is the emergence of hypertrophic cartilage, which is present in all skeletal elements that will develop a marrow cavity, e.g. long bones, hips, vertebrae, ribs, certain skull bones. The eventual replacement of cartilage by bone and marrow via EO relies on the sequential maturation of chondrocytes from resting, to proliferating, to hypertrophic (**Fig. 1A**). Chondrocyte hypertrophy manifests with a dramatic increase in cell size, cessation of proliferation, and synthesis of a new repertoire of differentiation-specific gene products (Godman and Porter 1960; Chan, D. and Jacenko 1998; Alvarez et al. 2001; James et al. 2010). Among these is the matrix protein collagen X, which represents the predominant biosynthetic product of hypertrophic cartilage (Gibson and Flint 1985; Schmid and Linsenmayer 1985). Concomitant with hypertrophy is a transformation from a non-calcified avascular cartilage matrix, to a calcifiable one that is permissive to vascular invasion. Morphometric analysis suggests that before vascular invasion, the terminal hypertrophic chondrocytes undergo either autophagy (Srinivas and Shapiro 2006; Bohensky et al. 2007) or apoptosis (Farnum and Wilsman 1989), the rate of which controls longitudinal growth of the skeletal element, as well as the transition from cartilage to trabecular bone and marrow (Farnum and Wilsman 1989).

Subsequent vascular entry into hypertrophic cartilage is critical to skeleto-hematopoietic development, since it leads to an influx of mesenchymal cells, hematopoietic precursors, and chondro/osteoclasts. This influx of cells, together with growth factors, cytokines and hormones, establishes the primary center of ossification and the marrow environment where hematopoiesis ensues (**Fig. 1**). Specifically, while chondro/osteoclasts degrade hypertrophic cartilage, multipotent stromal cells, including mesenchymal and perivascular reticular cells, form the marrow stroma, a meshwork of non-hematopoietic cells supporting hematopoiesis by providing structural scaffolding and producing hematopoietic factors (Taichman et al. 1996; Bianco et al. 1999). As hypertrophic cartilage continues to be degraded, matrix remnants serve as scaffolds upon which differentiating osteoblasts deposit bone matrix, thus forming trabecular bony spicules with hypertrophic cartilage cores (**Fig. 1B**) (Chan, D. and Jacenko 1998). Of note, the origin of the trabecular bone osteoblasts at the junction between marrow and the hypertrophic cartilage, termed the chondro-osseous junction, is still debated (Roach 1992; Roach et al. 1995; Roach and Erenpreisa 1996; Nakamura et al. 2006; Hilton et al. 2007; Maes et al. 2010). Following the formation of the primary ossification zones in the central or diaphyseal regions of skeletal elements, the establishment of secondary ossification centers at outer epiphyseal ends of bones defines the growth plate regions at the metaphysis (**Fig. 1A**). The growth plates occupy the narrow space that separates the marrow of the primary and secondary ossification centers, and are composed of a gradient of differentiating chondrocytes culminating in a zone of hypertrophic chondrocytes (**Fig. 1A & B**) (as reviewed in (Lefebvre and Smits 2005)). The continual replacement of the hypertrophic chondrocytes by trabecular bone and marrow allows for longitudinal skeletal growth, robust hematopoiesis, and the progression of EO without consumption of the skeletal model until maturity, when in most non-rodent vertebrates EO ceases and growth plates close (**Fig. 1C**) (Kilborn et al. 2002). Thus, the end result of EO is a porous network of primary trabecular bone, consisting of a hybrid hypertrophic cartilage-bone matrix, and engulfed by a hematopoietic marrow (**Fig. 1B & C**). Subsequent bone remodeling gradually leads to a complete replacement of the hybrid primary bone by mature secondary bone, and is coincident with a gradual decline in lymphopoiesis and the onset of immunosenescence (**Fig. 1C**) (as reviewed in (Compston 2002; Gruver et al. 2007)).

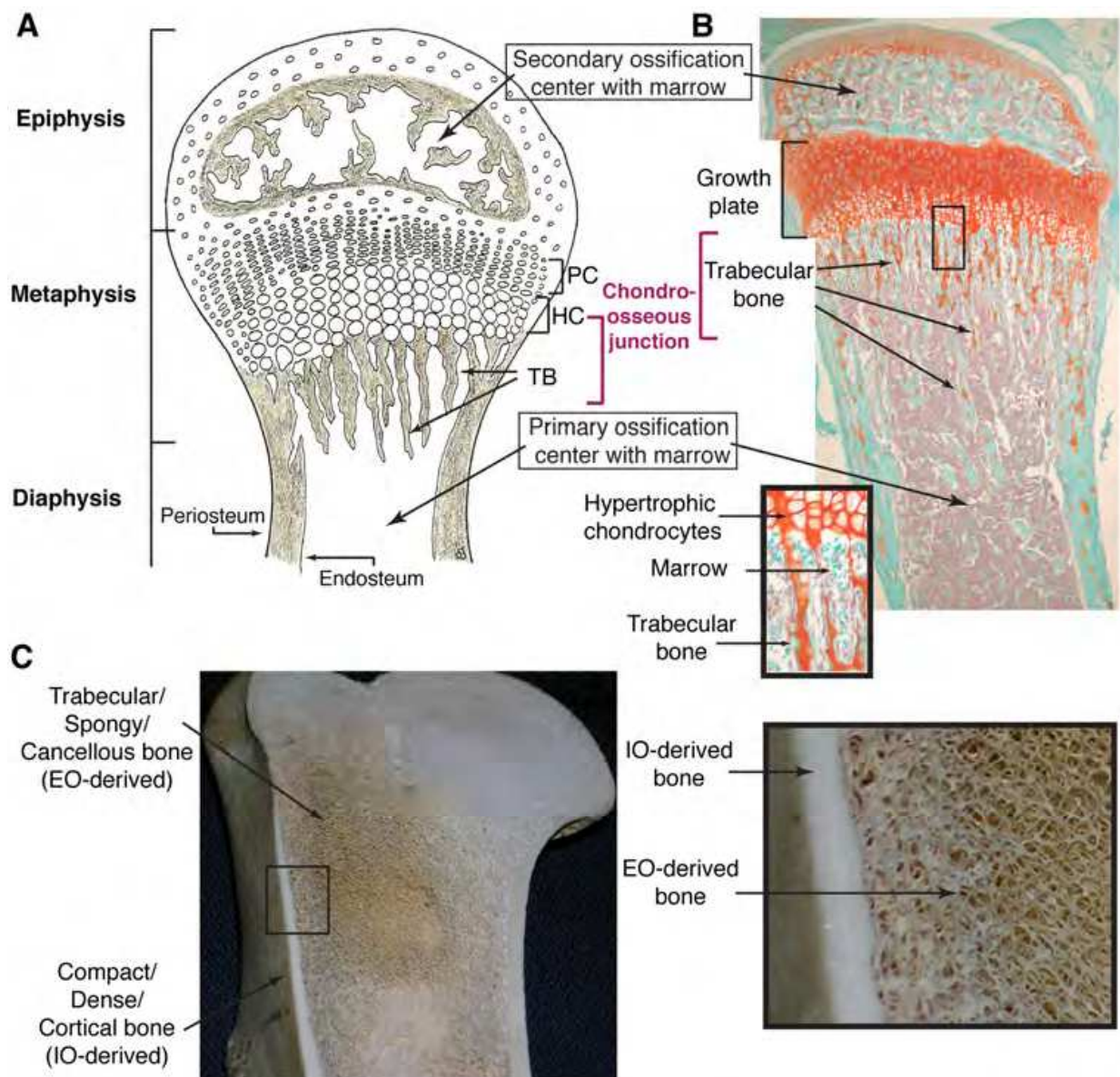


Fig. 1. Architecture of the endochondral bone. A) A schematic of a developing long bone illustrating its architecture. The epiphysis, or the bulbous end, lined by articular cartilage and containing the secondary ossification center with marrow, is supported by the flared metaphysis, which in turn rests upon the slender cylindrical shaft of the diaphysis. The growth plate separates the primary and secondary ossification centers, and consists of a gradient of differentiating chondrocyte zones; the proliferative cartilage (PC) and hypertrophic cartilage (HC) zones are marked, as well as the hybrid trabecular bone (TB) protruding into the marrow. The locations of the two-layered periosteal membrane surrounding the diaphysis and the inner endosteal network are marked. B) A longitudinal tibial section from a week-3 wild type mouse stained with safranin-orange, hematoxylin & eosin (H&E) and counterstained with fast green. Using these stains, the negatively charged cartilaginous matrix appears orange while the bone stains light blue-green; mature erythrocytes stain green, while other marrow elements stain pink-purple with H&E. The boxed inset is a high magnification of the chondro-osseous junction containing hypertrophic chondrocytes, bone and marrow with vasculature. The hybrid nature of the trabecular bone can

be appreciated by the orange staining of the cartilaginous core, with green-blue bone matrix deposited on the surface (magnification, 10x). C) The inorganic mineralized matrix of a mature zebra bone illustrates the structural differences between the EO-derived trabecular /spongy/cancellous bone and the IO-derived compact/dense/cortical bone. Boxed is a high magnification of the EO- and IO-derived bone tissues. Note the mesh-like structure of trabecular bone for hematopoietic cell support.

Taken together, the proper differentiation of chondrocytes, vascular invasion and the gradual replacement of the cartilaginous anlagen by trabecular bone and marrow through EO, underscore the intricate orchestration of skeleto-hematopoietic development. Moreover, the coincident establishment and localization of trabecular bone within the site of active hematopoiesis likely reflects a critical hematopoietic niche in the chondro-osseous region (**Fig. 1B boxed**) (Jacenko et al. 1993; Nilsson et al. 1997; Gress and Jacenko 2000; Nilsson et al. 2001; Jacenko et al. 2002; Yoshimoto et al. 2003; Arai, F. et al. 2004; Balduino et al. 2005; Sweeney et al. 2008; Kohler et al. 2009; Lo Celso et al. 2009; Xie et al. 2009; Sweeney et al. 2010). This skeleto-hematopoietic link is strongly supported by several animal models where alterations in process of EO leads to hematopoietic defects (**Table 1**), including mouse models with altered: collagen X (Jacenko et al. 1993; Gress and Jacenko 2000; Jacenko et al. 2002; Sweeney et al. 2008; Sweeney et al. 2010), parathyroid hormone related protein (PTHrP) receptor in osteoblasts (Calvi et al. 2001; Calvi et al. 2003; Kuznetsov et al. 2004; Wu et al. 2008), osteoblast numbers (Visnjic et al. 2001; Visnjic et al. 2004; Zhu et al. 2007), bone morphogenic protein (BMP) receptor type 1A in marrow cells (Zhang, J. et al. 2003), osteoclast function (Blin-Wakkach et al. 2004; Mansour et al. 2011), retinoic acid receptor gamma (Purton et al. 2006; Walkley et al. 2007), $G_s\alpha$ in osteoblasts (Wu et al. 2008), Dicer in osteoblasts (Raaijmakers et al. 2010), glypican-3 (Viviano et al. 2005), and perlecan (Rodgers et al. 2008). **Table 1** presents a list of mouse models with defects in hematopoiesis due to alterations in a component within the niche environment. Only those mouse models are summarized that were proven, by and large, via bone marrow transplantation experiments to have an aberrant niche environment, since wild type marrow cells could not rescue the disease phenotype of the host.

3. Overview of the hematopoietic niche

Hematopoiesis is the process by which hematopoietic stem cells (HSCs) generate and replenish progenitors that develop into fully mature blood and immune cells, and populate the periphery. During vertebrate ontogeny, hematopoiesis is established sequentially in several different anatomic sites (see Development of Hematopoietic Stem Cells chapter in this book for review). Coincident with the onset of EO (approximately the last third of embryonic development), hematopoiesis shifts from the fetal liver and spleen to the EO-derived marrow, which represents the predominant site of blood cell production after birth (Aguila and Rowe 2005; Cumano and Godin 2007). Therefore, the marrow has become a tissue of study for hematopoietic cell biology post parturition. Additionally, due to the ease of marrow cell isolation in combination with the extensive list of cell markers identifying HSCs at different stages of differentiation (as summarized in (Morrison and Spradling 2008)), stem cell niche biology has also utilized the marrow environment for study.

Year	Protein/ cell	Description	Hematopoietic highlights	References
1993	Collagen X	Collagen X is a short chain collagen secreted by hypertrophic chondrocytes in the growth plate of endochondrally developing bones. In these mice, collagen X is either knocked-out or mutated to cause dominant interference.	-Altered chondro-osseous junction -Decreased trabecular bone, -No change in HSPCs, -Decreased B lymphocytes throughout life, -Diminished immunity in vitro and in vivo, -Altered hematopoietic/lymphopoietic cytokines, e.g. decreased SCF, CXCL-12, IL-7, -Disease phenotype retained after transfer of wild type HSPCs into collagen X mice	Jacenko, 1993; Jacenko, 1996; Gress, 2000; Jacenko 2001; Jacenko 2002; Sweeney, 2008; Sweeney, 2010
2001	PTH/PTHrP receptor	Parathyroid hormone (PTH) and the PTH related protein (PTHrP) receptor (PPR) are involved in calcium homeostasis and activation of osteoblasts, thus indirectly osteoclasts. In these mice, a constitutively active form of PPR is expressed in mesenchymal cells under the 2.3kb promoter of collagen 1.	-Delayed hematopoiesis due to delay in the bone to marrow transition, -With aging, increased trabecular bone and osteoblast numbers, -Increased HSPCs, -Increase in Notch signaling, -Increase in IL-6, CXCL-12, SCF, -Decrease in B cells at all stages	Calvi, 2001; Calvi, 2003; Kuznetsov, 2004; Wu 2008
2001	Osteoblast deletion	Osteoblasts have been implicated as a niche cell where increased in osteoblasts resulted in increases in HSPCs. These mice were generated with the herpes thymidine kinase gene under the 2.3kb promoter of collagen for deletion of collagen I expressing mesenchymal cells after ganciclovir treatment.	-Loss of bone lining cells and trabecular bone elements, -Decrease in marrow cellularity, -Decreases in HSPCs, -Decreases in lymphoid, erythroid, and myeloid progenitor cells, -Decrease in osteoclasts, -Increased extramedullary hematopoiesis, -Recovery from disease phenotype after ganciclovir removed	Visnjic, 2001; Visnjic, 2004; Zhu, 2007
2003	BMPRI1A	The bone morphogenic protein receptor, type 1A (BMPRI1A) is a receptor for BMPs, which have been shown to influence hematopoiesis. These mice were generated with a PolyI:C-inducible Mx-1-Cre to delete BMPRI1A in hematopoietic and stromal cells.	-Increases in spindle-shaped N-cadherin+ CD45- osteoblasts (SNO), -Increases in HSPCs, -LT-HSC observed attached to SNO cells, -No block in HPC differentiation to the lymphoid or myeloid lineages	Zhang, 2003

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Table 1. Mouse models with altered hematopoietic niche environments.

Year	Protein/ cell	Description	Hematopoietic highlights	References
2004	Tcirg 1	The T cell immune regulator 1 (Tcirg1) is a subunit of the vacuolar protein pump (V-ATPase) involved in osteoclast resorption of bone. In these mice there is a mutation of Tcirg1 rendering osteoclasts ineffective at bone resorption.	-Increases in myelomonocytic differentiation, -Reduced medullary cavity size, -Defective B cell differentiation leading to reduced numbers, -Reduced interferon- γ secretion from T cells, -Decreased IL-7 secretion from bone marrow cells, -Rescue of phenotype with restoration of marrow environment after wild type cell transfer	Blin-Wakkach, 2004; Mansour, 2011
2005	Osteopontin	Osteopontin is an extracellular matrix glycoprotein made by several cell types, including osteoblasts, fibroblasts, chondrocytes, etc. In these mice, osteopontin is knocked-out, and in 1998 Rittling et.al. showed no alterations to bone morphology, but increased osteoclastogenesis.	-Increased number of HSPCs, -No change in lymphoid or myeloid cell production, -Decreased HSPC apoptosis, -Increased Jagged 1 and Angiopoietin 1 stromal expression, -Disease phenotype retained after transfer of wild type HSPCs to Opn ^{-/-} mice	Rittling, 1998; Stier, 2005; Nilsson, 2005
2005	p27Kip1 and MAD1	Cyclin-dependent kinase inhibitors MAD1 and p27Kip1 are negative regulators of cell cycle. In these two studies, mice had either p27Kip1 knocked-out (Chien, 2006) or p27Kip1 and MAD1 knocked-out (Walkley, 2005).	-Hyperplasia of hematopoietic organs, -Increased myeloid and erythroid colony forming cells, -Increase in LT-HSCs, -Disease phenotype retained after transfer of wild type HSPCs into p27Kip1 ^{-/-} mice	Walkley, 2005; Chien, 2006
2005	gp130	Glycoprotein 103 (gp130) is a subunit of the cytokine receptors for the IL-6 family. These mice were generated with the Tere mouse for excision of gp103 in hematopoietic and endothelial cells.	-Hypocellular marrow, -Impairment in erythro-and thrombopoiesis, -Reduction in T lymphocytes in the thymus, -Reduction of B lymphopoiesis in the marrow, -Extramedullary hematopoiesis, -Disease phenotype retained after transplant of wild type HSPCs into gp130 mice	Yao, 2005

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Table 1. continued

Year	Protein/ cell	Description	Hematopoietic highlights	References
2006	RAR gamma	Retinoic acid receptors (RAR) are nuclear hormone receptors that act as ligand-dependent transcriptional regulators. In these mice the RARgamma is knocked-out.	-Decrease in HSPCs, -Increased granulopoiesis, -Myeloproliferative-like disease with excessive extramedullary hematopoiesis, -Loss of trabecular bone by 12 weeks of age, -Disease phenotype retained after transfer of wild type HSPCs into RARγ ^{-/-} mice	Purton, 2006; Walkley, 2007
2007	Rb	Retinoblastoma protein (Rb) is a central regulator of the cell cycle and several downstream regulators have been shown to have effects on hematopoiesis. These mice were generated using an inducible deletion construct in conjunction with Mx-1 Cre for deletion of Rb in hematopoietic and stromal cells.	-Myeloproliferative disease phenotype, -Increased HSPC differentiation, -Egress of HSPCs from marrow to extramedullary sites, -Loss of Rb was found to be necessary from both the myeloid-derived cells and the environment for presentation of the disease phenotype	Walkley, 2007
2008	Gsa	Gsa is a heterotrimeric G protein subunit that activates the cAMP-dependent pathway by activating adenylate cyclase and is part of the parathyroid hormone (PTH) and the PTH related protein (PTHrP) receptor. In these mice, Gsa was ablated in cells expressing osterix, e.g. early osteoprogenitors and chondrocytes.	-Decreases in B cell precursors in the marrow and in the periphery, -No negative affect on other hematopoietic lineages, -Decreases in IL-7 expression from osteoblasts, -Decreases in trabecular bone, -Disease phenotype not transferable to wild type mice with marrow transplant	Wu, 2008
2008	Bis (BAG-3 or CAIR-1)	Bcl-2 interacting cell death suppressor (Bis) is a protein involved in antiapoptotic and antistress pathways. In this mouse, Bis was truncated for loss of function.	-Reduced lymphoid tissues, -Perturbed vasculature with defects in endothelial cells, -Loss of HSPCs, -Defect in B lymphopoiesis, -Decreased splenic hematopoietic cell numbers, -Defects in stromal progenitor cells, -Loss of stromal cells expressing CXCL-12 and IL-7, -Osteoblast lineage unaffected, -Disease phenotype retained after transplant of wild type cells into Bis ^{-/-} mice	Youn, 2008; Kwon, 2010

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Table 1. continued

Year	Protein/ cell	Description	Hematopoietic highlights	References
2008	Hf2/merlin	Neurofibromin 2 (Nf2)/moesin-ezrin-radixin-like (merlin) is a cytoskeletal scaffolding protein involved in cell-cell communications. These mice were generated with a PolyI:C-inducible Mx-1-Cre to delete Nf2/merlin in hematopoietic and stromal cells.	-Egress of HSPCs, -Hypocellular marrow, -Increases in marrow vascularity, -Hematopoietic lineages unaffected, -After time, increases in trabecular bone and osteoblast numbers accompanied by restoration in marrow cellularity, -Disease phenotype retained after transplant of wild type cells into Nf2/merlin mice	Larsson, 2008
2010	Dicer	Dicer is an endoribonuclease that cleaves double-stranded RNA and pre-miRNA into small interfering RNA. In these mice, Dicer was ablated in cells expressing osterix, e.g. early osteoprogenitors and chondrocytes.	-Decreases in leukocytes, platelets and red blood cells, -Decreases in B cell number with increases in myeloid cells, -No change in HSPC number, -Extramedullary hematopoiesis, -Slight decrease in osteoblast number with impaired differentiation, -Bone volume unchanged, but altered bone texture, -Disease phenotype retained after transplant of wild type cells into Dicer mice	Raaijmakers, 2010
2010	CAR cells	CXC chemokine ligand (CXCL) 12 abundant reticular (CAR) cells have been implicated as a hematopoietic niche cell in the marrow. These mice were designed to have inducible selective ablation of CAR cells with the diphtheria toxin receptor.	-Reduced cycling of lymphoid and erythroid progenitor cells, -Reduced HSPC numbers, -HSPCs more quiescent, -HSPCs express more myeloid genes, -No changes in osteoblasts or endothelial cells, -Impaired production of SCF and CXCL-12	Omatsu, 2010
2010	Nestin ⁺ cells	Nestin is an intermediate filament protein expressed in nerve cells and reported here in rare non-hematopoietic cells with mesenchymal progenitor cell qualities. These mice were generated using the inducible diphtheria toxin with Nes-creERT2 for selective depletion of nestin expressing cells.	-Rapid reduction of HSPCs in marrow and increase in HSPCs in spleen, -Reduction of adrenergic nerve fibers, -Reduction of wild type HSPC homing to marrow of Nestin mice	Mendez-Ferrer, 2010

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Table 1. continued

Year	Protein/ cell	Description	Hematopoietic highlights	References
2010	Ebf2	Early B cell factor 2 (Ebf2) is a transcription factor expressed in neurons, immature osteoblasts and adipocytes. In these mice, Ebf2 is knocked-out.	-Impaired lymphopoiesis, -Reduced numbers of HSPCs, -Mice were smaller than wild type cohorts, -Disease phenotype rescued after transplant of Ebf2 ^{-/-} cells into wild type mice	Corradi, 2003; Kieslinger, 2010
2011	Agrin	Agrin is a heparan sulfate proteoglycan matrix protein expressed on MSCs and trabecular osteoblasts in the niche. In these mice, agrin expression is deficient with low levels of muscle specific kinase (MuSK) expression for postnatal survival.	-Marrow hypoplasia with decreases in myeloid and lymphoid cells, -Reduced CD45 ⁺ cell numbers in marrow, spleen and marrow, -Decreases in thymus T-lineage populations, -Decreases in ST-HSC in marrow, but normal levels in fetal liver, -Disease phenotype is not transferred to wild type mice after transplant with MuSK-L: Agrin ^{-/-} hematopoietic cells	Mazzon, 2011

Table 1. continued

The idea of a unique tissue environment, or stem cell niche, as a tissue setting that can direct progenitor cell behavior, e.g. quiescence, proliferation, differentiation, etc. was proposed over four decades ago (Wolf and Trentin 1968; Trentin 1971; Schofield 1978; Wolf 1979). Hematopoietic niches, or hematopoietic microenvironments (HME), are defined by the association of particular cell types, their secreted matrix products and their soluble hematopoietic factors (Yin and Li 2006; Rodgers et al. 2008). The identity of the cellular, matrix and soluble components that influence HSCs, including the long-term populating (LT-HSC), short-term populating (ST-HSC), or the more differentiated hematopoietic progenitor cells (HPC), as well as the lymphoid and myeloid lineages, remains an active topic of investigation. However, at least two hematopoietic niches have been described, an osteoblastic (or endosteal) niche, ascribed to osteoblasts residing on bone surfaces, and a vascular niche, ascribed to endothelial cells and subendothelial MSCs or pericytes lining marrow sinusoids. Many have argued that more quiescent LT-HSCs and ST-HSCs are located in the osteoblast niche, while differentiating HPCs are located in the vascular niche for mobilization to the periphery (Lord et al. 1975; Shackney et al. 1975; Gong 1978; Nilsson et al. 2001; Heissig et al. 2002; Arai, F. et al. 2004; Balduino et al. 2005; Jang and Sharkis 2007; Bourke et al. 2009). However, these regions in the marrow are so close in proximity (Arai, F. et al. 2004; Kiel et al. 2005; Lo Celso et al. 2009; Xie et al. 2009), that the osteoblast and vascular niches may be the same, or perhaps interchangeable to some degree. Additionally, recent work has identified other cells involved in hematopoiesis that do not fully comply with these proposed niche regions, such as CXC chemokine ligand (CXCL)-12 expressing reticular cells that are scattered throughout the marrow (Tokoyoda et al. 2004; Sugiyama et al. 2006; Omatsu et al. 2010). Below we will discuss the different cellular, matrix and soluble components within the marrow that have been shown to influence hematopoiesis.

3.1 Cells of the niche

Experiments designed to identify the cells of the HME date back over fifty years (Pfeiffer 1948; Tavassoli and Crosby 1968; Tavassoli and Weiss 1971; Meck et al. 1973; Friedenstein et al. 1974; Tavassoli and Khademi 1980; Friedenstein et al. 1982; Patt et al. 1982; Tavassoli 1984; Friedenstein et al. 1987; Gurevitch and Fabian 1993; Kawai et al. 1994; Kuznetsov et al. 1997; Hara et al. 2003; Akintoye et al. 2006; Mankani et al. 2007; Sacchetti et al. 2007; Chan, C.K. et al. 2008; Mankani et al. 2008; Song et al. 2010). In these studies, ectopic bone with a functional HME was generated in host mice using various bone marrow derived osteoprogenitor seed cells. More recently, different osteoprogenitor pools have been isolated that can either generate EO-like bone with active hematopoiesis or compact IO-like bone without an HME (Akintoye et al. 2006; Chan, C.K. et al. 2008). Collectively, these studies have shown that functional HMEs form through the progression of EO with contributions from cartilage, bone, vasculature, and marrow stromal cells. Further, similar conclusions about the necessity of EO-derived components, e.g. cells and matrix molecules, were obtained through analyses of several mouse models with skeleto-hematopoietic defects (**Table 1**), including mice with disrupted collagen X function in the HME (Jacenko et al. 1993; Gress and Jacenko 2000; Jacenko et al. 2002; Sweeney et al. 2008; Sweeney et al. 2010). Discussed below are the data describing which cell type(s), associated matrix and soluble factors are necessary for blood cell development in the marrow, including: multipotent stromal cells (fibroblasts, pericytes, reticular cells, and adipocytes), osteoblasts, chondrocytes, endothelial cells, and cells of hematopoietic origin (hematopoietic stem/progenitor cells (HSPC), osteoclasts and macrophages).

3.1.1 Fibroblasts and perivascular cells

As early as the 1970's, *in vitro* studies with marrow stromal adherent colonies showed that this pool of cells is able to support hematopoiesis (Friedenstein et al. 1970; Dexter et al. 1973; Friedenstein et al. 1974; Friedenstein et al. 1976; Dexter et al. 1977). These plastic adherent colonies have been thought to contain mesenchymal progenitor cells, and likely mesodermal progenitor cells as well (Petrini et al. 2009). This would account for recent data indicating that marrow derived progenitor cells generate adipocytes, chondrocytes and osteoblasts, traditional mesenchymal cell types, as well as fibroblasts, smooth muscle cells, endothelial cells, and pericytes/subendothelial cells (Bentley and Foidart 1980; Muguruma et al. 2006; Sacchetti et al. 2007; Crisan et al. 2008; Kalajzic et al. 2008; Augello et al. 2010; Mendez-Ferrer et al. 2010). Thus, isolated marrow stromal cells will be referred to as multipotent stromal cells (MSC) throughout (Horwitz et al. 2005). The MSCs isolated for ectopic bone assays have been described as osteoprogenitor cells that generate bone with a HME able to support host-derived hematopoiesis (Kuznetsov et al. 1997; Akintoye et al. 2006; Sacchetti et al. 2007; Chan, C.K. et al. 2008; Morikawa et al. 2009). Of note, many of these osteoprogenitor cells have been shown to have stem-like qualities, such as self-replication and the ability to differentiate into several different cell types. For example, Sacchetti et al. isolated human-derived MCAM/CD146-expressing subendothelial cells, which can self-replicate as well as give rise to osteoblasts, chondrocytes and reticular cells in ectopic HMEs (Sacchetti et al. 2007). More recently, these data were replicated in the mouse by Morikawa et al. who also identified a perivascular cell type that has the ability to self-replicate and give rise to adipocytes, osteoblasts, chondrocytes and endothelial cells (Morikawa et al. 2009). An

additional perivascular cell has also been identified as a HME cell type, the nestin-expressing MSCs (Mendez-Ferrer et al. 2010). These, nestin⁺ MSCs have been shown to be spatially associate with HSPCs in the marrow and to express several HSPC maintenance genes, e.g. CXCL-12, stem cell factor (SCF)/kit ligand, angiopoietin (Ang)-1, interleukin (IL)-7, vascular cell adhesion molecule (VCAM)-1, and osteopontin (Mendez-Ferrer et al. 2010). Further, numbers of HSPC were rapidly reduced in the marrow of mice that were selectively depleted of nestin⁺ MSCs (**Table 1**) (Mendez-Ferrer et al. 2010). These mouse models also revealed a necessity for marrow nestin⁺ MSCs for homing of transferred HSPCs (Mendez-Ferrer et al. 2010). Together, these data suggest that MSCs and associated daughter cells not only make up the physical structure of the HME, but also provide maintenance and differentiation signals to HSPCs.

3.1.2 CXCL-12 abundant reticular cells

Reticular cells are of mesodermal origin and are a type of fibroblast cell localized to the intertrabecular region of the marrow near both the osteoblast and vascular niches (Weiss 1976; Rouleau et al. 1990). Recently, a sub-set of marrow reticular cells has been shown to express high levels of CXCL-12 (or stromal derived factor (SDF)-1) and have been termed CXCL-12 abundant reticular (CAR) cells (Tokoyoda et al. 2004; Sugiyama et al. 2006). CXCL-12 is reportedly involved in several aspects of hematopoiesis, including HSPC homing and maintenance, as well as B cell development (Nagasawa et al. 1994; Nagasawa et al. 1996; Ara et al. 2003; Broxmeyer et al. 2005; Jung et al. 2006; Sugiyama et al. 2006). Using CXCL-12/GFP knock-in mice, HSPCs, early lineage B cells and plasma B cells have been shown to spatially associate with CAR cells (Tokoyoda et al. 2004), suggesting CAR cells are a HME cell type. To address the importance of CXCL-12 expressing cells in the HME, Omatsu et al. designed a mouse model with selective ablation of CAR cells (**Table 1**) (Omatsu et al. 2010). These assays showed no change in the osteoblast or vascular niches, but impaired production of SCF and CXCL-12, combined with marked reduction in cycling lymphoid and erythroid progenitors. Further, the HSPC population in these mice was more quiescent, diminished in numbers and expressed myeloid selector genes. Finally, CAR cells can give rise to adipocytes and osteoblasts (Bianco et al. 1988; Balduino et al. 2005; Sipkins et al. 2005; Omatsu et al. 2010). Thus, these data combined with the ectopic bone assays and the nestin⁺ reticular cell studies discussed above, raise the possibility that the CAR, osteoprogenitor and nestin⁺ cells are from a similar cell pool, sharing differentiation capabilities and roles in hematopoietic support.

3.1.3 Adipocytes

Within the young marrow there are few adipocytes, however this phenomenon is reversed with aging and after marrow insult, such as post irradiation (Burkhardt et al. 1987; Verma et al. 2002). Although adipocytes have been described as having a positive influence on hematopoiesis via growth factors secretion (Lanotte et al. 1982), other studies have reported that these growth factors are in too low a concentration to influence HSPCs and that adipocytes secrete anti-hematopoietic factors as well (Hotamisligil et al. 1993; Zhang, Y. et al. 1995; Yokota et al. 2000; Corre et al. 2006; Belaid-Choucair et al. 2008; Miharada et al. 2008). Further, an increase in marrow adiposity has been negatively correlated with hematopoiesis in vivo (Touw and Lowenberg 1983; Naveiras et al. 2009). Interestingly,

Naveiras et al. have shown that in the adult mouse spine there is a proximal to distal gradient of marrow adiposity, with thoracic vertebrae being virtually free of adipocytes. This provides an *in vivo* model to study the effects of adipocytes on hematopoietic cells under homeostatic conditions. These studies showed that the number, frequency and cycling capacity of HSPCs was reduced as the number of adipocytes was increased (Naveiras et al. 2009). In support, after irradiation and marrow transplantation of mice genetically incapable of forming adipocytes, or in wild type mice treated with an inhibitor of adipogenesis, there was enhanced HSPC expansion compared to non-treated wild type cohorts (Naveiras et al. 2009). Of note, in these models of reduced/abrogated adipogenesis, as well as in a model where the fatty marrow is surgically removed, the increase in hematopoiesis is concomitant with an increase in bone formation (Tavassoli et al. 1974; Naveiras et al. 2009). These data suggest that after marrow insult and in the absence of adipocytes, there are signals enhancing osteoblast activity and bone formation, which may contribute to the enhanced hematopoiesis measured, as discussed below. This is supported by the clinical observations that aged patients have an increase in adiposity in the marrow, which is correlated with a decrease in bone formation and decreased hematopoiesis (Verma et al. 2002; Rossi et al. 2005; Mayack et al. 2010).

3.1.4 Osteoblasts

With the identification of osteoblast-like cells in stromal cultures (Friedenstein et al. 1987; Benayahu et al. 1991; Benayahu et al. 1992) and osteoprogenitors within marrow preparations for ectopic bone assays (Kuznetsov et al. 1997; Akintoye et al. 2006; Sacchetti et al. 2007; Chan, C.K. et al. 2008; Morikawa et al. 2009), Emerson and Taichman designed *in vitro* assays to assess the ability of isolated osteoblasts to support hematopoiesis (Taichman and Emerson 1994; Taichman et al. 1996; Taichman et al. 1997; Jung et al. 2005; Jung et al. 2006; Zhu et al. 2007). These assays showed that osteoblasts can support hematopoiesis through the secretion of pro-hematopoietic cytokines, e.g. granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CXCL-12, IL-6, and IL-7, and that cell-cell contact is necessary for support via integrin binding (very late antigen (VLA)-4/5 and VCAM/ICAM). Further, these assays confirmed a connection between osteoblasts and B cell development. To assess the contribution of osteoblasts to hematopoiesis *in vivo*, several different mouse models have been generated that either increase osteoblasts (Calvi et al. 2001; Calvi et al. 2003; Zhang, J. et al. 2003), decrease osteoblasts (Visnjic et al. 2001; Visnjic et al. 2004), disrupt EO-based trabecular bone formation (Jacenko et al. 1993; Gress and Jacenko 2000; Jacenko et al. 2001; Jacenko et al. 2002; Sweeney et al. 2008; Sweeney et al. 2010), alter osteoblast signaling (Wu et al. 2008), or modify osteoblast RNA processing (**Table 1**) (Raaijmakers et al. 2010). These *in vivo* models have confirmed that osteoblasts can support hematopoiesis, are involved in B lymphopoiesis, make pro-hematopoietic cytokines, make cell-cell contact with HSPCs, and moreover, have implicated osterix expressing osteoprogenitors as mediators of hematopoiesis.

The above studies, as well as many imaging studies of HSPC in bone, support the osteoblast hematopoietic niche theory and suggest that the osteoblast niche may additionally encompass the B lymphopoietic niche (Nilsson et al. 1997; Nilsson et al. 2001; Yoshimoto et al. 2003; Arai, F. et al. 2004; Balduino et al. 2005; Kohler et al. 2009; Lo Celso et al. 2009; Xie et

al. 2009). For instance, Xie et al. showed that GFP⁺ HSPCs home to the trabecular bone surface in the marrow, and others have reported early developing B lymphocytes at the endosteal region of the marrow (Hermans et al. 1989; Jacobsen and Osmond 1990; Osmond 1990; Xie et al. 2009). This zone is the chondro-osseous region where hypertrophic chondrocytes, trabecular osteoblasts and marrow cells are juxtaposed (**Fig. 1**). Hypertrophic chondrocytes and their matrix components are also essential for trabecular bone formation, and are proposed to be part of the osteoblast/lymphopoietic niche (Jacenko et al. 2002; Rodgers et al. 2008; Sweeney et al. 2008; Sweeney et al. 2010). Interestingly, hypertrophic chondrocytes have been described to trans-differentiate into osteoblasts (Roach 1992; Galotto et al. 1994; Roach et al. 1995; Roach and Erenpreisa 1996), and express osteoblast-like markers, e.g. osterix, osteocalcin, osteonectin, osteopontin and collagen I (Roach 1992; Yagi et al. 2003), suggesting similarities in the cells of the chondro-osseous niche. Indeed, it has been suggested that chondro-osteoprogenitor cells that expresses the chondrocyte-like marker collagen II contribute to both the perichondrial and trabecular osteoblast populations (Nakamura et al. 2006; Hilton et al. 2007). In contrast, however Maes et al. do not report any contribution from the collagen II labeled hypertrophic chondrocytes to trabecular bone (Maes et al. 2010). Taken together, these findings are reminiscent of the reports indicating that progenitor cells in the marrow can give rise to different cell types with many similarities, e.g. osteoprogenitors, CAR and nestin⁺ cells not only share gene expression profiles, but are all located in the chondro-osseous environment (Weiss 1976; Rouleau et al. 1990; Sugiyama et al. 2006). The possible overlap between the cells of the chondro-osseous region can also be appreciated when comparing osteoblasts and reticular cells that can support B lymphopoiesis and both express VCAM-1 and IL-7 (Ryan et al. 1991; Funk et al. 1995; Zhu et al. 2007). Moreover, using an osteoblast lineage tracer mouse generated with an osterix-LacZ construct, cells of the perichondrium, trabecular bone, cartilage and marrow stroma, some intimately associated with blood vessels in a pericyte-like fashion, were all positive for osterix expression (Maes et al. 2010), again confirming an overlap of cell phenotypes in the chondro-osseous HME.

3.1.5 Chondrocytes

As previously discussed, chondrocytes provide the blueprint for future bone with a marrow cavity during EO, and are adjacent to the postulated osteoblast and vascular niches (**Fig. 1B boxed**) (Arai, F. et al. 2004; Kiel et al. 2005; Kohler et al. 2009; Xie et al. 2009). Indeed, growth plate chondrocytes, as well as osteoblasts and vascular cells, express leukemia inhibitory factor (LIF), which can synergize with growth factors to promote the proliferation of HSPCs (Keller et al. 1996; Grimaud et al. 2002). Additionally, Wei et al. recently showed that hypertrophic chondrocytes express CXCR-4, the receptor for CXCL-12 made by stromal cells and osteoblasts (Peled et al. 1999; Kortesisidis et al. 2005; Dar et al. 2006; Jung et al. 2006; Sacchetti et al. 2007; Wei et al. 2010). These data begin to reveal the cross talk between the hypertrophic chondrocytes and the cells of the chondro-osseous environment that are players within the hematopoietic niche, e.g. osteoblasts, stromal and hematopoietic cells.

To date, no imaging studies have attempted to localize HSPCs to hypertrophic chondrocytes. However, the contribution of various matrix components, in particular the heparan sulfate proteoglycans (HSPG), in establishing reservoirs of soluble factors for cell signaling and/or retention of HSPCs has been well established (as reviewed in (Rodgers et

al. 2008) also see (Gordon et al. 1988; Roberts et al. 1988; Siczkowski et al. 1992; Verfaillie 1993; Allouche and Bikfalvi 1995; Bruno et al. 1995; Klein et al. 1995; Gupta et al. 1996; Gupta et al. 1998; Borghesi et al. 1999; Siebertz et al. 1999; Zweegman et al. 2004; Rodgers et al. 2008; Spiegel et al. 2008). In support, our laboratory has shown altered localization of both hyaluronan and HSPGs within the hypertrophic cartilage zone of the growth plates in the collagen X mouse models that display altered hematopoiesis (Jacenko et al. 2001), which directly links EO and the hypertrophic cartilage matrix to hematopoiesis (Jacenko et al. 1993; Gress and Jacenko 2000; Jacenko et al. 2001; Jacenko et al. 2002; Sweeney et al. 2008; Sweeney et al. 2010). Briefly, collagen X is a short chain, network forming collagen that is the major secreted matrix protein of hypertrophic chondrocytes and is localized to the hypertrophic cartilage/chondro-osseous region (Campbell et al. 2004), where it is proposed to form a hexagonal lattice-like network in the matrix (Jacenko et al. 1991; Chan, D. and Jacenko 1998). Affinity co-electrophoresis studies demonstrated that collagen X and heparin, a structural analog of heparan sulfate, can endogenously bind (Sweeney, unpublished). We thus proposed that the hypertrophic chondrocyte derived matrix, made up of the collagen X network that is likely stabilized by associating with the HSPGs, is enriched with hematopoietic factors and is a vital component of the HME (Jacenko et al. 2001; Rodgers et al. 2008). In accord, mouse models where the function of collagen X was altered via transgenesis or targeted gene knock-out have both an altered HME structure, as well as aberrant hematopoiesis. Specifically, alterations within the EO-derived chondro-osseous junction include aberrant growth plate histomorphometry, collapsed hypertrophic chondrocyte matrix network, diminished and altered localization for HSPG within hypertrophic cartilage and trabecular bone, and decreased trabecular bone. The hematopoietic changes include diminished B lymphopoiesis throughout life, perinatal lethality within a sub-set of mice due to opportunistic infections by the third week of life, decreased responses to concanavalin A by splenocytes from mice at all ages, and the succumbing of all collagen X mice to non-virulent pathogen challenge (**Table 1**) (Jacenko et al. 1993; Rosati et al. 1994; Jacenko et al. 1996; Kwan et al. 1997; Gress and Jacenko 2000; Jacenko et al. 2001; Jacenko et al. 2002; Sweeney et al. 2008; Sweeney et al. 2010). Additionally, altered levels of hematopoietic cytokines have been measured from the collagen X mouse derived hypertrophic chondrocytes and trabecular osteoblasts when compared to wild type cohorts (Sweeney, 2011 *Ann N Y Acad. Sci.* in press). The altered cytokine availability may negatively affect hematopoiesis, which may be even further amplified by the altered chondro-osseous matrix in the collagen X mice, e.g. loss of functional collagen X and diminished HSPGs at the chondro-ossous HME (Jacenko et al. 2001). In support of the notion that matrix/cytokine signaling can affect cell differentiation in the HME, fate switching was sited as the cause of decreased osteoblast progenitors and bone formation in a knock-out mouse for the critical transforming growth factor (TGF)- β binding proteoglycans, biglycan and decorin (Bi et al. 2005). Overall, the collagen X mouse models have highlighted the contribution of EO-derived cells and matrix components to HMEs and to hematopoietic cell development.

3.1.6 Endothelial cells

Marrow arterioles and capillaries supply the sinusoids, which in turn supply the marrow with cells and nutrients (reviewed in (Kopp et al. 2005)). These are the sites of the vascular niche, and examples of active vascular niches can be appreciated during development when

hematopoiesis takes place in the yolk sac, aorta-gonad-mesonephros region and placenta perivascularly (Cumano et al. 1996; Medvinsky and Dzierzak 1996; Sanchez et al. 1996; de Bruijn et al. 2002; North et al. 2002; Gekas et al. 2005; Ottersbach and Dzierzak 2005). Additionally, throughout life in some species, such as the zebra fish, hematopoiesis is not coincident with bone (Murayama et al. 2006). Further, the characteristics of the marrow sinusoids, e.g. chemokine and adhesion molecule expression, not only allow them to be conduits for hematopoietic cells to and from the circulation, but also to serve as an area for HSPC differentiation (Rafii et al. 1994; Rafii et al. 1995; Schweitzer et al. 1996; Naiyer et al. 1999; Abkowitz et al. 2003; Avezilla et al. 2004). In agreement, endothelial cells from several sources are able to support HSPC maintenance and differentiation toward lymphoid and myeloid lineages in culture (Rafii et al. 1995; Ohneda et al. 1998; Li et al. 2004; Wittig et al. 2009; Butler et al. 2010). Visualizing the vascular niche in vivo with a pure sub-set of HSCs also provided support for the vascular niche theory. These studies revealed approximately 60% of HSC residing in the chondro-osseous HME, and of that population, approximately 60% were proximal to the vasculature, where as 15% were near bone (Kiel et al. 2005). Moreover, one aspect of the osteoblast niche theory maintains that HSCs are bound to osteoblasts by a N-cadherin-mediated homophilic adhesion, however in a mouse model where HSC specific N-cadherin was depleted, hematopoiesis was fully functional (Zhang, J. et al. 2003; Kiel et al. 2009). More in vivo support is provided by the biglycan deficient mice, which present with decreased trabecular osteoblasts and bone formation, however show no defects in hematopoiesis, HSC frequency or function, and show HSC localization to the vasculature (Kiel et al. 2007). These data suggest an overlap in niche location with perhaps some ability for compensation between the osteoblast and vascular niches, albeit limited. In support, via histochemistry of the long bone, one can appreciate the spatial proximity of osteoblasts to the vasculature (**Fig. 1B boxed**).

3.1.7 Hematopoietic derived cells influence the niche

Discussed above are the data linking non-hematopoietic cells with hematopoiesis, however there are also data supporting reciprocal affects of hematopoietic derived cells influencing non-hematopoietic lineages. For example, HSPCs regulate MSC differentiation toward the osteoblast lineage via expression of BMP-2 and -6, suggesting that the HSPCs can actively maintain the osteoblast niche (Jung et al. 2008). Additionally, macrophages intercalated throughout bone have been described as osteoblast helper cells since they promote osteoblast mineralization in vitro and form a canopy over osteoblasts generating bone in vivo (Chang et al. 2008). An additional player in osteoblastogenesis is the megakaryocyte. In mouse models with increased numbers of megakaryocytes due to maturation arrest, increased osteoblast proliferation and bone mass were measured (Kacena et al. 2004). Additionally, megakaryocytes have been described as niche restoring cells post-irradiation since they migrate to the damaged bone surfaces and increase local concentrations of CXCL-12, platelet-derived growth factor (PDGF)- β and basic fibroblast growth factor (bFGF), which are associated with osteoblast proliferation (Kacena et al. 2006; Dominici et al. 2009).

A reciprocal balance between bone deposition by osteoblasts, bone resorption by osteoclasts and signaling by osteocytes is extensively noted in the literature, and is appreciated clinically. These coupled interactions will not be discussed here other than to acknowledge

that the function of one cell type highly depends upon and is affected by the actions of the other (Khosla 2003). Thereby, the continual signaling between cells of the mesenchymal and hematopoietic lineages underlies the tightly coupled process of bone remodeling, and its uncoupling can lead to skeletal disorders such as osteoporosis, osteopetrosis, as well as calcium homeostasis imbalances. Such examples are also seen in mouse models; for example, in one model where osteoclasts are depleted, instead of having increased bone mass due to lack of resorption, there is decreased bone mass compared to wild type cohorts (Kong et al. 1999). Collectively, the intricate cross talk between cells within the HME can both positively and negatively affect the niche environment as well as hematopoiesis, and is a vast area of research that remains to be adequately explored.

3.2 Soluble factors and the extracellular matrix in the niche

3.2.1 Cytokines, chemokines, growth factors, and neurotransmitters

As referred to above, the hematopoietic and non-hematopoietic cells within the HME are surrounded in all dimensions by matrix components and soluble factors. The building blocks of the extracellular matrices found within the chondro-osseous environment can include collagens, proteoglycans (PGs; including the HSPGs) and their glycosaminoglycan (GAG) constituents and glycoproteins. Collagens generally provide structural support for cells in the niche by forming supramolecular aggregates around cells (Jacenko et al. 1991), while the PGs, such as the HSPGs, can trap and store soluble factors for presentation to local cells (as reviewed in (Rodgers et al. 2008)). The amount and ratio of these molecules in the matrix also dictates the mechanical properties of the HME, which has recently become a topic of investigation in the stem cell field. For instance, matrix elasticity in the HME can influence fate choices of HSPCs (Holst et al. 2010), a phenomenon also reported with MSCs (as reviewed in (Discher et al. 2009)). Thus, the matrix provides structural integrity to the HME, acts as a substrate for cell migration and anchorage, and actively regulates cell morphology, development and metabolic function (Peerani and Zandstra 2010). The cells in the HME receive information for maintenance, development, differentiation, etc. via cell-cell interactions, cell-matrix interactions, and exposure to variable concentrations and combinations of soluble factors, e.g. cytokines, chemokines, hormones, and growth factors. Many soluble factors have been implicated in hematopoiesis, such as CXCL-12, SCF, Fms-related tyrosine kinase 3 ligand (Flt-3L), thrombopoietin (TPO), FGF, G-CSF, GM-CSF, LIF, Wnt, BMP-4, IL-3, 6, 7, 8, 11, 12, 14, 15 (Guba et al. 1992; Heinrich et al. 1993; Verfaillie 1993; Funk et al. 1995; Rafii et al. 1997; Taichman et al. 1997; Peled et al. 1999; Majumdar et al. 2000; Ponomaryov et al. 2000; Petit et al. 2002; Avecilla et al. 2004; Kortessidis et al. 2005; Dar et al. 2006; Jung et al. 2006; Spiegel et al. 2007; Wittig et al. 2009), or in maintenance and quiescence of HSCs, e.g. Ang-1 and TGF (Eaves et al. 1991; Fortunel et al. 2000; Arai, F. et al. 2004) (cytokine functions reviewed in (Zhang, C.C. and Lodish 2008)). The HME cell types discussed above are the primary sources of these soluble factors, however lymphocytes have also been shown to stimulate and suppress hematopoiesis through the release of different factors during both homeostasis and immune activation (Nathan et al. 1978; Bacigalupo et al. 1980; Mangan et al. 1982; Harada et al. 1985; Trinchieri et al. 1987; Crawford et al. 2010). Interestingly, many of these soluble factors are sequestered and presented by the matrix, specifically HSPGs, which have been described as key orchestrators of hematopoiesis (Bruno et al. 1995; Gupta et al. 1996; Gupta et al. 1998; Borghesi et al. 1999). This is particularly

relevant to the collagen X mouse models that present with a disrupted collagen X network coupled with a decreased HSPG staining intensity at the chondro-osseous HME and diminished cytokine levels, leading to diminished B lymphopoiesis (Gress and Jacenko 2000; Jacenko et al. 2001; Jacenko et al. 2002; Sweeney et al. 2008; Sweeney et al. 2010). These findings imply that the structural defects in the matrix may lead to changes in the cytokine reservoirs, which in turn would negatively affect hematopoietic cell development. By extension, human diseases associated with altered matrix components at the HME may have altered hematopoiesis due to changes in cytokine availability, such as with Simpson-Golabi Behmel syndrome where alterations in the HSPG glypican-3 results in skeletal and hematopoietic abnormalities (Pilia et al. 1996; Viviano et al. 2005).

There is increasing evidence that the nervous system can also affect the immune system through neurotransmitter signaling. The bone and marrow are supplied with autonomic efferent and afferent sensory innervations, specifically at the epiphysis and metaphysis of long bone, which includes the chondro-osseous HME (**Fig. 1A**) (reviewed in (Mignini et al. 2003)). Catecholamines, acetylcholine and peptide transmitters of neural and non-neural origin are released in the HME, which contribute to neuro-immune modulations. For example, signaling from the nervous system can regulate HSPC egress and repopulation of the marrow (Katayama et al. 2006; Spiegel et al. 2007), which has been shown to be coupled to the circadian rhythm (Mendez-Ferrer et al. 2008). Indeed, HSPCs have receptors for several neurotransmitters, which can stimulate cell proliferation (Spiegel et al. 2008; Kalinkovich et al. 2009). Of note, beta-adrenergic agonists have been shown to stimulate osteoclast activity (Arai, M. et al. 2003), which could have an effect on the osteoblast niche via two methods, a) physically by decreasing bone lining cells and releasing HSPCs, and b) chemically via the release of soluble factor (Kollet et al. 2006; Mansour et al. 2011). Calcium is an example of one such soluble factor, which serves as an attractant to HSPCs encouraging homing to the osteoblast niche (Adams et al. 2006). Hematopoietic cell egress from the marrow has also been linked to many systemic causes, including exercise, inflammation, bleeding, cytotoxic drugs, and psychological anxiety (reviewed in (Lapid et al. 2008)). These data serve as reminders that hematopoiesis and the HME can be influenced by factors outside of the local environment.

3.2.2 Cell and matrix influence

In the HME, cell-cell interactions influence cell fate decisions and mobility/homing; examples of such interactions include: Notch-1/Jagged-1, N-cadherin/N-cadherin and VLA-4/VCAM-1 (reviewed in (Coskun and Hirschi 2010)). On the other hand, cell-matrix interactions influence not only cell behavior, but also cell anchorage to the niche. To date, the matrix proteins within the HME include: collagens (Types I, II, III, IV and X), glycoproteins (fibronectin, laminin, nidogen, tenascin C, thrombospondin, vitronectin), PGs (perlecan, decorin, agrin) and the GAG hyaluronan (Bentley and Foidart 1980; Bentley 1982; Spooner et al. 1983; Zuckerman and Wicha 1983; Zuckerman et al. 1985; Klein 1995; Ohta et al. 1998; Campbell et al. 2004; Mazzon et al. 2011). These matrix constituents can signal to hematopoietic cells through cell receptors such as: integrins, immunoglobulin-like molecules, cadherins, selectins, and mucins (Teixido et al. 1992; Coulombel et al. 1997; Levesque and Simmons 1999; Zhang, J. et al. 2003; Merzaban et al. 2011). Notably, the HME matrix network is not static, but is continually remodeled by different enzymes including

metalloproteinases, neutrophil elastase and heparinase. Matrix turnover can thus assist in the release of hematopoietic cells from the niche (Levesque et al. 2001; Heissig et al. 2002; Petit et al. 2002; Spiegel et al. 2008), as well as liberate bound soluble hematopoietic factors (Heissig et al. 2002; Spiegel et al. 2008). An example of one such cell-matrix interaction in the HME is the VLA-4/fibronectin binding between HSPCs and the matrix, which provides the hematopoietic cell with anchorage as well as proliferation stimuli (Weinstein et al. 1989; Klein et al. 1998; Sagar et al. 2006). Hyaluronan also impacts HSPC maintenance, propagation, homing and homeostasis via CD44 binding (Avigdor et al. 2004; Matrosova et al. 2004; Haylock and Nilsson 2006). Most recently, Mazzon et al. have found the binding between agrin, expressed by trabecular osteoblasts and MSCs in the niche, and HSPCs leads to survival and proliferation signals (Mazzon et al. 2011). Finally, mature plasma B cells homing back to the marrow via CXCL-12 signals are anchored to their marrow niche via matrix-bound ligands produced by local myeloid cells (O'Connor et al. 2004; Crowley et al. 2005; Ingold et al. 2005; Moreaux et al. 2005; Nagasawa 2006; Schwaller et al. 2007; Huard et al. 2008; Moreaux et al. 2009). In fact, it has been shown that this interaction maintains long-lived antibody producing plasma B cells in the marrow by stimulating expression of anti-apoptotic genes in the lymphocytes (O'Connor et al. 2004; Huard et al. 2008). Thus, the cell-matrix interactions in the marrow serve to support hematopoietic maintenance and development, as well as support the persistence of mature hematopoietic cells that have returned to the marrow.

4. Summary and perspectives

All the specialized cells of the blood are generated through hematopoiesis via the directed differentiation of HSCs. The bone marrow, which is the predominant hematopoietic tissue after birth (Aguila and Rowe 2005; Cumano and Godin 2007), is formed through EO, where the cartilage anlage serves as a transient template for trabecular bone, and defines the environment of the marrow stroma. Thereby, either directly or indirectly, the process of EO establishes the hematopoietic niche by providing the niche with both the structure matrix constituents and the cellular components (Jacenko et al. 1993; Taichman and Emerson 1994; Taichman et al. 1996; Taichman et al. 1997; Gress and Jacenko 2000; Calvi et al. 2001; Visnjic et al. 2001; Jacenko et al. 2002; Calvi et al. 2003; Zhang, J. et al. 2003; Visnjic et al. 2004; Jung et al. 2005; Jung et al. 2006; Zhu et al. 2007; Chan, C.K. et al. 2008; Sweeney et al. 2008; Wu et al. 2008; Raaijmakers et al. 2010; Sweeney et al. 2010). Many cell types, matrix components and soluble factors contribute to the HME (**Fig. 2**). Through several different methods, HSPCs have been visualized in the chondro-osseous HME (Nilsson et al. 1997; Nilsson et al. 2001; Yoshimoto et al. 2003; Arai, F. et al. 2004; Balduino et al. 2005; Kiel et al. 2005; Kohler et al. 2009; Xie et al. 2009), which is comprised of vasculature sinusoids, sympathetic nerves, complex and diverse matrix regions, as well as osteoblasts, hypertrophic chondrocytes, endothelial cells, pericytes, CXCL-12 expressing cells, adipocytes, nestin⁺ cells, MSCs, macrophages intercalated in the endosteum, and cells of the immune system, both developing and recirculating. The cells of the HME express the cytokines, growth factors and chemokines utilized throughout hematopoiesis, as well as the matrix molecules that provides structural support, cell-matrix signaling and reservoirs of soluble factors (**Fig. 2**). We propose that the chondro-oseous HME is not static, but is continuously changing in response to various systemic influences (Lapid et al. 2008), as well as to remodeling of the hybrid trabecular bone-hypertrophic cartilage spicules into mature secondary bone (**Fig. 1C & 2**). During remodeling of the HME, both cells and

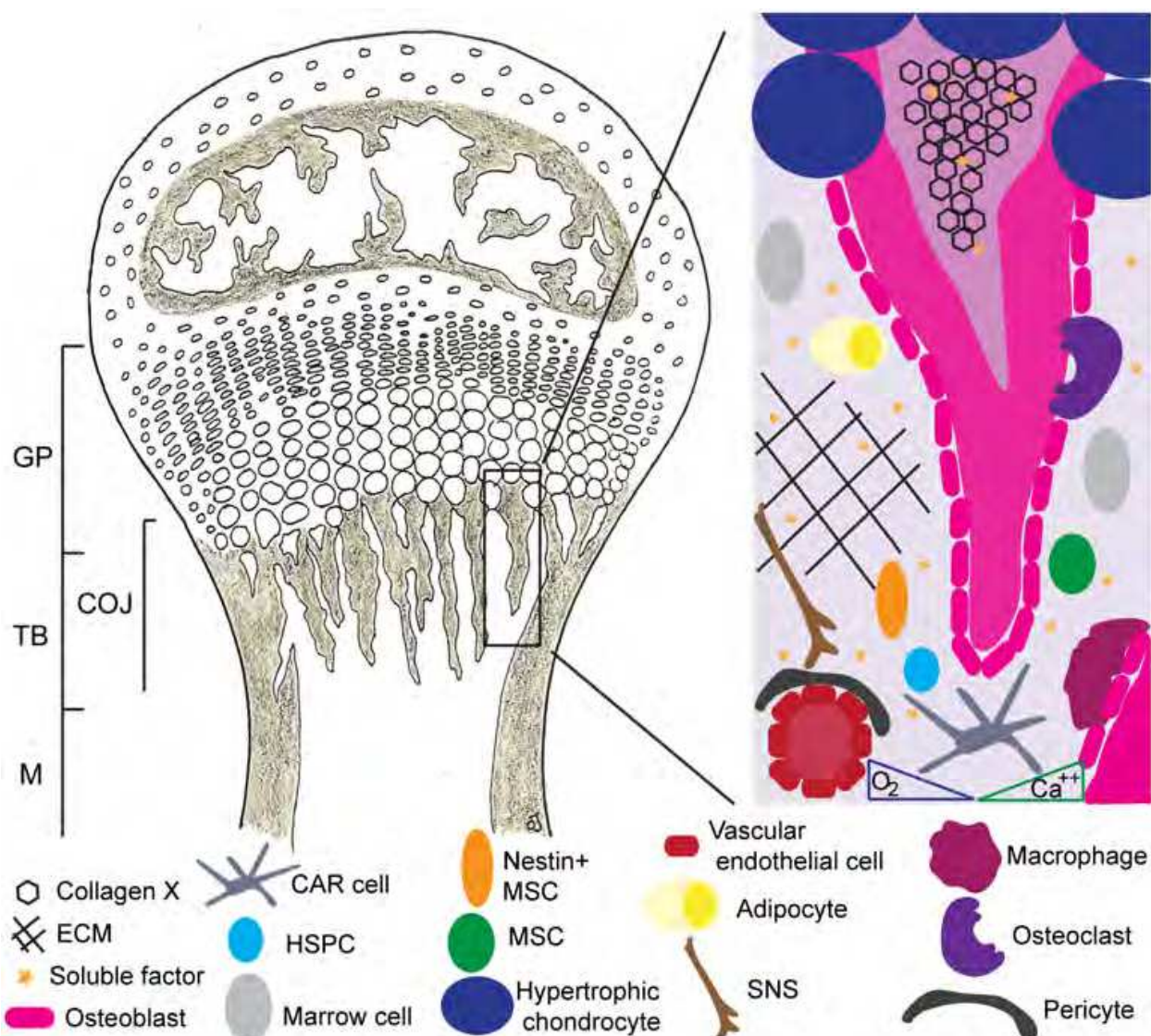


Fig. 2. The cells, matrix components and soluble factors within the chondro-osseous hematopoietic microenvironment. The putative hematopoietic niche has been localized to the chondro-osseous junction (COJ) of endochondrally developing bones, e.g. the juncture of the growth plate (GP) hypertrophic chondrocytes and the trabecular bone (TB) and marrow (M). Boxed, a cartoon in higher magnification represents the chondro-osseous hematopoietic environment, which includes: osteoblasts, hypertrophic chondrocytes, endothelial cells, pericytes, CXCL-12 abundant cells (CAR), adipocytes, endosteal intercalating macrophages, and other marrow cells, such as lymphocytes. Additionally, progenitor cells such as hematopoietic stem/progenitor cells (HSPC), multipotent stromal cells (MSC) and nestin expressing (nestin +) MSC are represented. All of these cells serve as a source of secreted factors, including cytokines, chemokines and growth factors, as well as neurotransmitters from the sympathetic nervous system (SNS). Also note the gradients of oxygen (O_2) and calcium (Ca^{++}) released from the vasculature or remodeled bone respectively. Finally, the extracellular matrix (ECM) in the marrow and in the core of trabecular bone, consisting of hypertrophic cartilage derived lattice-like collagen X and HSPGs, can serve as a substrate for cell anchorage, migration, and/or signaling through cell-ECM binding and as a reservoirs of secreted factors.

soluble factors are released into the milieu; for example matrix degrading enzymes release HSPCs for egress, and the combined activity of osteoclasts and enzymes release soluble factors from bone, including the trabecular bone with a collagen X/HSPG core (**Fig. 2**). Thus, the chondro-osseous HME is a continually active site with intrinsic and systemic signals influencing the cellular cross talk that ensures proper quiescence, maintenance, and differentiation of the HSPCs.

As itemized in **Table 1** and discussed above, various mouse models have revealed important cell and matrix players in the HME, while others have implicated the importance of proper cell cycle (Walkley et al. 2005; Walkley et al. 2007), transcription (Corradi et al. 2003; Purton et al. 2006; Walkley et al. 2007; Kieslinger et al. 2010), cell-cell communication (Larsson et al. 2008), and survival signals (Youn et al. 2008; Kwon et al. 2010) in the HME (**Table 1**). Still, the exact cellular make up and location of the HME is continually under debate, though most agree the cells of the osteoblast and vascular niches are important players in hematopoiesis. The possibility of osteoblast and vascular niches spatially overlapping or having the ability to provide some compensation for each other to some extent, is another intriguing theory. Evidence for this is observed with the biglycan deficient mouse model that presents with reduced bone, yet intact hematopoiesis (Kiel et al. 2007), as well as with the recently identified CAR cells that unite the osteoblast and vascular niches in the chondro-osseous HME by the observation that they are in contact with 90% of HSPCs throughout the trabecular bone region and the marrow sinusoidal region (Sugiyama et al. 2006; Omatsu et al. 2010). Additionally, there is similarity in the expression of hematopoietic soluble factors between the osteoblasts, endothelial cells, and CAR cells, such as CXCL-12 implicated in the homing, growth, development and maintenance of hematopoietic cells (Peled et al. 1999; Ponomaryov et al. 2000; Tokoyoda et al. 2004; Broxmeyer et al. 2005; Kortessidis et al. 2005; Dar et al. 2006; Sugiyama et al. 2006). Moreover, Medici et al. have confirmed an endothelial to osteoblast and chondrocyte transition *in vivo*, further supporting a cell interchange and overlap theory (Medici et al. 2010). In contrast, there is also evidence that the osteoblast and vascular niches provide different roles in hematopoiesis, e.g. a quiescence and maintenance role versus a differentiation and egress role (Lord et al. 1975; Shackney et al. 1975; Gong 1978; Nilsson et al. 2001; Heissig et al. 2002; Arai, F. et al. 2004; Balduino et al. 2005; Jang and Sharkis 2007; Bourke et al. 2009). Further, although these niches are proximal in the chondro-oseous region, mathematical modeling has predicted a layer of only two myeloid cells is sufficient to deplete most oxygen provided by a near by sinusoid (Chow et al. 2001). Thus, the local environment within each niche may differ significantly in chemical signals, such as with oxygen and calcium (**Fig. 2**).

Overall, the research generated in the hematopoietic niche field is beginning to shed light on many hematologic disorders, such as myelodysplasia, myeloproliferative syndromes and leukemias that seem to be influenced by the quality of the marrow environment (Walkley et al. 2007; Walkley et al. 2007; Raaijmakers et al. 2010). Further information on niche components, specifically the matrix molecules, will assist in generating bio-mimicking composites necessary for *in vitro* culture and expansion of patient specific hematopoietic tissues, for such clinical applications as autologous marrow transfers. The past sixty years of hematopoietic biology research has increased our understanding of marrow stromal cell types, as well as the three-dimensional regions that provide structure and organization of cell signaling for the maintenance and propagation of HSPCs. The study of the

hematopoietic niche will continue to provide details on necessary niche components, which may assist in the understanding of other stem cell niches, including the vascular, skin, hair, and neural niches, and provide therapeutic cues for immuno-osseous diseases that present with skeletal defects and altered hematopoiesis, such as McKusick type metaphyseal chondrodysplasia (cartilage-hair hypoplasia; CHH), Shwachmen-Diamond syndrome, Schimke dysplasia (Spranger et al. 1991; Kuijpers et al. 2004; Hermanns et al. 2005), and others.

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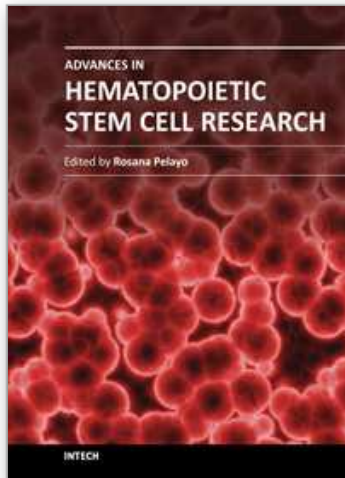
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