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Review Article

Congenital disorders of bone and blood

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ABSTRACT

Bone and marrow are the two facets of the same organ, in which bone and hematopoietic cells coexist and interact. Marrow and skeletal tissue influence each-other and a variety of genetic disorders directly targets both of them, which may result in combined hematopoietic failure and skeletal malformations. Other conditions primarily affect one organ with secondary influences on the other. For instance, various forms of congenital anemias reduce bone mass and induce osteoporosis, while osteoclast failure in osteopetrosis prevents marrow development reducing medullary cavities and causing anemia and pancytopenia. Understanding the pathophysiology of these conditions may facilitate diagnosis and management, although many disorders are presently incurable. This article describes several congenital bone diseases and their relationship to hematopoietic tissue.

Contents

1. Introduction

Bone and hematopoietic tissue are linked and therefore disturbance of one is often accompanied by reciprocal disruption of the other [1]. For example, congenital diseases of marrow may alter bone mass or induce skeletal malformations [1]. In this article, we will provide insight as to how congenital disorders of bone or hematopoiesis affect each other.

2. The bone-bone marrow organ

Bone is not isolated as it directly interacts with marrow and, via endocrine signals, with distant tissues such as fat [2], kidney [3] and brain [4]. Marrow is hosted in the medullary cavity delimitated by the bone (Fig. 1). Medullary cavities extend throughout the entire skeleton [5], making this apparatus strong but light, and allowing at the same time the vital functions of a friable organ that must be protected, such as the marrow [6].

Marrow appears at the 11th week of human embryonic development, concomitant with the appearance of bone tissue [7]. This co-occurrence supports the concept that these tissues are interdependent both anatomically and functionally. Furthermore, the discovery that

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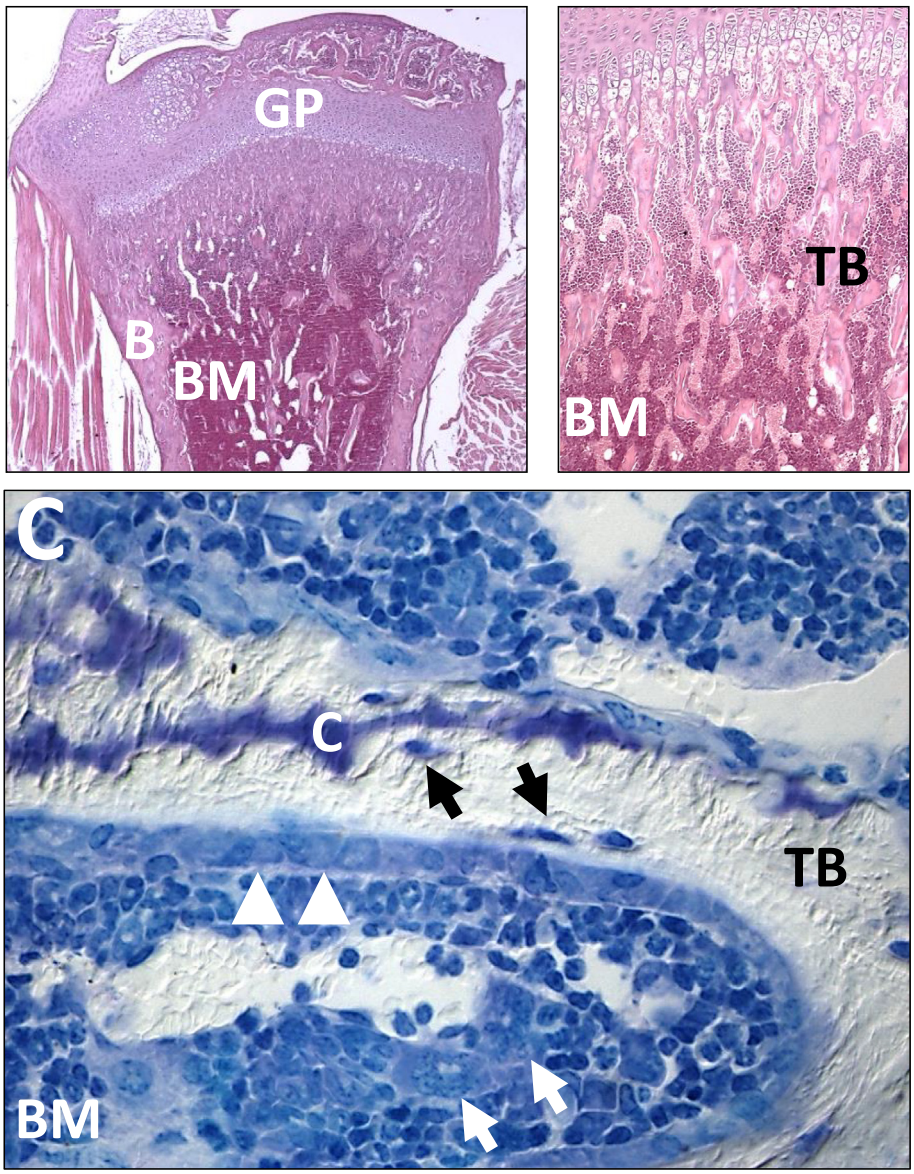

Fig. 1. The bone-bone marrow organ. Histological sections of mouse tibias. (A) Low magnification image showing the overall structure of the bone-bone marrow organ and the intimate relationship between the skeletal and the hematopoietic tissue. Hematoxylin/Eosin (H&E) staining. Original magnification 10×. (B) Intermediate magnification of the mouse tibia spongiosa showing the trabecular bone intermingled with the hematopoietic bone marrow. H&E staining. Original magnification 20×. (C) High magnification of the bone-bone marrow organ showing the bone and bone marrow cells. Toluidine blue staining. Original magnification 100×. GP: growth plate; B: cortical bone; BM: bone marrow; TB: trabecular bone; C: cartilage; white arrowheads: osteoblasts; white arrows: osteoclasts; black arrows: osteocytes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

both hematopoietic and mesenchymal stem cells are geographically associated in the same hematopoietic environment [8,9] has opened the door to new concepts. In fact, it is now posited that bone and marrow are two facets of the same organ [10], which, like other organs, have a capsule, a stroma and a parenchyma. Stroma and parenchyma have histological features similar to other parenchymal organs: i) a vascularized reticular tissue hosting the stromal cells, (which also include the osteogenic lineage), their progenitors and stem cells (mesenchymal stem cells) [9]; ii) a parenchyma represented by hematogenous cells at all stages of development, including myeloid and, to a certain extent, lymphoid lineages [8]. Adipocytes are also lodged in marrow parenchyma. In contrast, the capsule is unique. In fact, whereas in all other organs the capsule is composed of fibrous connective tissue proper, marrow is surrounded by a specialized and mineralized connective tissue: the bone (Fig. 1A, B). The interaction between the bone and hematopoietic tissue [8] is reflective of the fact that bone cells originate in marrow and not in the bone per se. In fact, both mesenchymal and hematopoietic stem cell lineages generate bone cells [11,12]. Specifically, mesenchymal stem cells are the progenitors of bone forming osteoblasts and their mature product, namely osteocytes [10,12]. Alternatively, hematopoietic stem cells, committed to myeloid lineage, give rise to bone resorbing osteoclasts [11]. Thus, disorders that affect the mesenchymal and/or hematopoietic compartments may disturb bone formation, resorption or both, with substantial clinical consequences [1].

3. Congenital diseases

Congenital diseases may be genetically determined, idiopathically induced or caused by injuries during development. Non-genetic causes may reflect maternal drug administration, infection, hormonal imbalance or trauma. For example, in the mid twentieth century, **thalidomide**, a drug administered to treat the morning sickness during the first three months of pregnancy, induced embryopathy in about 10,000 children who presented at birth with malformed limbs [13]. A

Table 1
Congenital bone-blood disorders. Symptoms and pattern of inheritance.

Disease	Bone defects	Blood defects	Other symptoms	Inheritance	References
Aase-Smith syndrome	Triphalangeal thumbs Cleft palate Severe join contractures	Underdeveloped bone marrow Anemia	Hydrocephalus Deformed ears Ptosis Impaired mouth full opening	Not hereditary in most cases Autosomal recessive in 45% of patients	[49,51]
Baller-Gerold syndrome	Short stature Craniosynostosis Radial ray hypoplasia	Fanconi anemia	Cardiac disease Renal failure Anal defects	Autosomal recessive	[30–32]
Bent bone dysplasia syndrome	Bent long bones Poorly mineralized calvaria Cranyosynostosis Midface hypoplasia Hypoplastic pubis and clavicles Facial deformities Midface hypoplasia Prematurely erupted teeth Micrognathia Small growth plate hypertrophic chondrocytes Thin periosteum with hypercellularity	Hepatosplenomegaly and ectopic hematopoiesis in one case	Low-set ears Hypertelorism	Autosomal recessive	[62,63]
Cartilage-hair hypoplasia	Dwarfism Immune deficiency Metaphyseal chondrodysplasia Unusual flexibility of some joints Difficult elbow full extension	Rare autoimmune disorders Recurrent infections	Hypotrichosis Thin and hypopigmented hairs Skin hypopigmentation Malformed nails and teeth Risk of skin basal cell carcinoma, leukemia and lymphoma Gastrointestinal disorders Constipation Enlarged colon Anal stenosis Esophageal atresia	Autosomal recessive	[38–40]
Diamond-Blackfan anemia	Short stature Osteopenia Forearm anomalies Flatness of the hand palm (thenar eminences) Malformed thumbs	Anemia	Cataracts Glaucoma Strabismus Kidney abnormalities Cardiac defects Opening of urethra in males Decreased radial pulsation	Autosomal recessive Autosomal dominant X-linked Sporadic	[18,29–52]
Fanconi anemia	Short stature Hypoplasia or aplasia of the radii and thumbs Craniofacial defects	Bone marrow malfunction	Uncontrolled cell growth Predisposition to acute myeloid leukemia	Autosomal recessive	[20–25]
Ghosal type hemato-diaphyseal dysplasia	Diaphyseal dysplasia Large medullary cavities in long bones	Hemato-dipahyseal and –metaphyseal dysplasia Bone marrow fibrosis and hypocellularity Pancytopenia	Fatigue	Autosomal recessive	[72–74]
Hereditary myeloproliferative disorders (Agnogenic myeloid metaplasia or Familial infantile myelofibrosis)	Osteosclerosis	Fibrotic bone marrow Ectopic hematopoiesis Leukoerythroblastosis Tear-drop cells (dacrocytes)	Leukemia	Autosomal recessive	[55,56]
Histiocytosis- lymphadenopathy plus syndrome:				Autosomal recessive	[57–60]
Rosai-Dorfman	Short stature Joint deformities	Polyclonal hypergammaglobulinemia Generalized lymphadenopathy	Sensorineural hearing loss Swellings of eyelids that contain histiocytes		
Faisalabad histiocytosis	Medullary bone solitary or multifocal lytic areas	Polyclonal hypergammaglobulinemia Massive lymphadenopathy Inflammation		Non-hereditary, but recently reported in identical twins	
Oculo-oto-radial syndrome - IVIC	Radial ray hypoplasia	Fanconi anemia		Autosomal dominant	[44–47]
Okihiro (or Duane radial ray) syndrome	Radial ray hypoplasia	Trombocytopenia	Optic nerve hypoplasia Deafness Imperforate anus	Autosomal dominant	[44,45]
Osteogenesis imperfecta	Short stature Fragile bones Multiple fractures Loose joints	Mild bleeding tendency Abnormal platelet aggregations and adhesion to collagen	Blue sclerae Haring loss Respiratory problems Artery dissentions	Autosomal recessive Autosomal dominant	[64–69]

(continued on next page)

Table 1 (*continued*)

Disease	Bone defects	Blood defects	Other symptoms	Inheritance	References
	Tooth problems	Impaired release of platelet factor 3	Altered energy metabolism and impaired ATP/ADP metabolism		
Osteopetrosis	High bone mass Fragile bones with multiple fractures Reduced bone cavities Osteomyelitis Lack of tooth eruption	Anemia Pancytopenia Ectopic hematopoiesis Fibrotic bone marrow in osteoclast-rich forms	Susceptibility to infections Loss of hearing and vision Primary neurodegeneration in some cases	Autosomal recessive Autosomal dominant X-linked	[106–114]
Rapadilino syndrome	Short stature Underdevelopment or absence of the bones of the forearm and the thumbs	Fanconi anemia	Difficult feeding Diarrhea Vomiting Increased frequency of osteosarcoma	Autosomal recessive	[37]
Rothmund-Thompson syndrome	Small stature Tooth abnormalities Absent or malformed bones Fused bones Osteopenia Osteoporosis Osteopetrosis (rare) Radial ray malformation	Neutropenia	Skin rash Skin atrophy Telangiectasias Sparse hairs, eyebrows and eyelashes Growth retardation Nail abnormalities Chronic diarrhea Vomiting	Autosomal recessive	[33–37]
Schwachman-Diamond syndrome	Osteopenia Metaphyseal dysostosis especially in femurs Short stature Craniofacial abnormalities Syndactyly	Bone marrow failure Neutropenia Cytopenia	Exocrine pancreas insufficiency Myelodysplastic syndrome Leukemia	Autosomal recessive	[18,53,54]
Severe congenital neutropenia	Osteopenia Osteoporosis Growth retardation	Neutrophil deficiency Recurrent infections of sinuses, lungs and liver Myelodysplastic syndrome	Seizures Heart and genital abnormalities Leukemia	Autosomal recessive X-linked	[76–83]
Sickle cell disease	Osteopenia Osteoporosis Osteonecrosis Osteomyelitis Vitamin D deficiency	Hemolytic anemia	Vaso-occlusive syndrome Tissue injury Organ damage	Autosomal recessive	[1,89–96]
Thalassemia	Osteoporosis	Anemia	Hypogonadotrophic hypogonadism Delayed puberty Deficiency of growth hormone and IGF-1 Renal insufficiency Iron toxicity Increased RANKL/OPG ratio Hypoparathyroidism Vitamin D deficiency Hypothyroidism Diabetes	Autosomal recessive	[84–92]
Thrombocytopenia with absent radii	Bilateral radius aplasia	Hypomegakariocytic thrombocytopenia	Gut and cardiac diseases	Autosomal dominant	[41,43]
VACTERL+H syndrome	Vertebral anomalies Limb anomalies Triphalangeal thumbs	Bone marrow malfunction	Cardiac disease Anal atresia Tracheoesophageal fistula Renal dysfunction Hydrocephalus,	Autosomal recessive X-linked	[1,27,28]
WT limb-blood syndrome	Radialulnar hypoplasia Bifid or hypoplastic thumbs	Fanconi anemia	Leukemia Lymphoma Cutaneous syndactyly	Autosomal dominant	[48]

subset of these patients developed phocomelia, characterized by the absence of the proximal portion of one or more limbs, with hands or feet attached to the trunk by a small abnormal bone [14]. Recent evidence associates **maternal diabetes** with a high incidence of developmental bone defects, including lumbosacral agenesis and hypoplastic and absent femurs [15,16], while **Toxoplasma gondii** induces intracranial calcifications [17].

Hereditary bone disorders may also involve **hematopoietic tissue**, and a number of hematopoietic disorders, some of which are congenital, are equally deleterious to bone health [1,18] (Table 1). In the past, severe hematopoietic diseases were not investigated for their skeletal related events given that they were rapidly lethal in infancy. Present treatment, however, may extend life expectancy and make skeletal consequences relevant to the individual morbidity.

4. Congenital hematologic anomalies with bone malformations

A number of hereditary hematologic diseases affect also skeletal patterning and are accompanied by skeletal malformations [1]. They represent defects of the limb bud before osteogenesis occurs and a recurrent theme is that they are caused by cellular damages, for instance due to

Table 2
Genes involved in congenital blood-bone disorders.

Disease	Genes frequently implicated	Gene products
Aase-Smith syndrome	Unknown	Protein associated with correct synthesis of ribosomal protein
Baller-Gerold syndrome	*RECQL4*	RecQ helicase
Rapadilino syndrome		
Rothmund-Thompson syndrome		
Bent bone dysplasia syndrome	*FGFR2*	Fibroblast growth factor receptor 2
Cartilage-hair hypoplasia	*RMRP*	Noncoding RNA of the mitochondrial RNA-processing endoribonuclease (RNase MRP)
Diamond-Blackfan anemia	*RPS19*	Ribosomal protein 19
Fanconi anemia	*FANCA*	Complementation group A protein
	FANCC	Complementation group C protein
	FANCG	Complementation group G protein
Ghosal type hemato-diaphyseal dysplasia	*TBXAS1*	Thromboxane synthase 1
Hereditary myeloproliferative disorders (Agnogenic myeloid metaplasia; Familial infantile myelofibrosis)	Unknown	Unknown
Histiocytosis-lymphadenopathy plus syndrome (Faisalabad histiocytosis; Rosai-Dorfman disease)	*SLC29A3*	Equilibrative nucleoside transporter 3
Oculo-oto-radial syndrome – IVIC	*SALL4*	Spalt-like transcription factor 4
Okihiro (or Duane radial ray) syndrome		
Osteogenesis imperfecta	*COLL1a1*	Collagen 1 α chain
	COLL1a2	Collagen 1 a2 chain
	CRTAP	Cartilage associated protein
	P3H1	Prolyl-3 hydroxylase 1
Osteopetrosis	*TCIRG1*	a3 Subunit V-H^+-ATPase
	CLCN-7	Chloride channel 7
	OSTM1	Osteopetrosis-associated transmembrane protein 1
	SNX10	Sorting nexin 10
	PLEKHM1	Pleckstrin homology domain-containing family M member 1
	CAII	Carbonic anhydrase type II
	TNFSF11	Receptor activator of NF-κB ligand
	TNFRSF11A	Receptor activator of NF-κB
	NEMO	NF-kappa-B essential modulator
Rothmund-Thompson syndrome	*C16orf57*	U6 snRNA phospho-diesterase
Schwachman-Diamond syndrome	*SBDS*	Highly conserved ribosomal maturation protein
Severe congenital neutropenia	*ELANE*	Neutrophil elastase
	HAX1	HS-1-associated protein X-1
	CSF3R	Colony stimulating factor 3 receptor
	G6PC3	Glucose-6-phosphatase catalytic subunit 3
	GFI1	DNA-binding zinc finger transcription factors Gfi1
	G6PC3	Glucose-6-phosphatase
	JAGN1	ER transmembrane protein Jagunal homolog 1
	TCIRG1	a3 subunit V-H^+-ATPase
	VPS45	Vacuolar sorting protein 45
	WAS	Wiskott-Aldrich syndrome protein
Sickle cell disease	*HBB*	β-globin
Thalassemia	*HBA*	α-globin
	HBB	β-globin
Thrombocytopenia with absent radii	1q21 microdeletion plus *RBM8A* SNP[a]	RNA-binding motif protein 8A
VACTERL+H syndrome	*FANCA*	Complementation group A protein
	FANCB	Complementation group B protein
	FANCC	Complementation group C protein
	FANCD1	Complementation group D1 protein
	FANCE	Complementation group E protein
	FANCG	Complementation group G protein
WT limb-blood syndrome	Unknown	Unknown

[a] SNP, Single Nucleotide Polymorphism.

failures in the DNA repair pathways, that at an early stage of development preferentially leads to radial ray malformations [19].

For example, patients with **Fanconi anemia** may exhibit forearm deformities [20]. (Table 1). The disease is autosomal recessive and caused by mutations of genes expressed within the "Fanconi anemia pathway" (Table 2). It is characterized by predisposition to bone marrow malfunction as well as increased susceptibility to cancer [21]. The Fanconi pathway is induced when DNA replication is blocked because of damage of the DNA, especially due to interstrand cross-links. The pathway triggers DNA repair and induces continuation of DNA replication [22]. The molecular mechanism relies on a complex of 8 proteins, two of which (FANCD2 and FANCI) transport DNA repair proteins to the interstrand cross-links, promoting their removal [22]. At least 15 genes cause the disease. Most patients display mutations of *FANCA*, *FANCC* and *FANCG* genes (Table 2) that impair formation of the Fanconi pathway [23], predominantly affecting rapidly proliferating cells such as those of hematopoietic lineages [24,25]. Disruption of these cells generates pancytopenia [26]. Furthermore, Fanconi gene mutations can lead to uncontrolled cell growth, which predisposes patients to acute myeloid leukemia [20]. Fanconi patients also display skeletal malformations including short stature, limb anomalies, especially hypoplasia or aplasia of radii and thumbs, as well as craniofacial defects [1]. Whether a common mechanism causes bone malformations and impairs hematopoiesis is not known.

VACTERL + H, is a rare Fanconi-like variant with suggested autosomal recessive or X-linked inheritance [27] (Table 1). This condition is characterized by vertebral anomalies, radial dysplasia and other limb abnormalities, including triphalangeal thumbs [1]. Patients are also predisposed to cardiac disease, anal atresia, tracheoesophageal fistula, renal dysfunction and hydrocephalus (VATER phenotype) [1]. The VATER phenotype had been reported in Fanconi anemia of complementation groups A, C, D1, E, G, while the X-linked VACTERL + H is associated with mutations in the *FANCB* gene [28] (Table 2). Similar to Fanconi diseases, patients with VACTERL + H have hematological anomalies [28].

Several congenital diseases are associated with mutations of the *RECQL4* gene encoding the RecQ helicase (Table 2), an enzyme that temporarily unwinds the two DNA strands to allow replication or DNA repair. This "genome caretaker" [29] is expressed by many cell types and is essential for the development of bone and skin.

Baller-Gerold syndrome displays forearm malformations, craniosynostosis and radial ray hypoplasia [30] (Table 1). It has been proposed that exposure, in utero, to sodium valproate, a drug used to treat epilepsy, bipolar disorders, migraine and seizure, can cause the disease, which, may represent a heterogeneous phenotype of variable etiology [31]. However, some patients are affected by mutations of the *RECQL4* gene [32], whereas others have a phenotype reminiscent of the

Rothmund-Thompson syndrome, also due to mutations of the *RECQL4* gene [33] (Tables 1, 2). Patients with this latter condition have rash progressively extending from cheeks to arms and legs, skin atrophy, telangiectasias (so-called poikiloderma) as well as sparse hairs, eyebrows, and eyelashes. They experience retarded growth, tooth and nail abnormalities, chronic diarrhea and vomiting [34]. Many of them develop skeletal abnormalities, including absent, malformed or fused bones and low bone mineral density (osteopenia or osteoporosis). Alternatively, rare cases are associated with an osteopetrosis-like syndrome [35] due to mutations in the *C16orf57* gene encoding the U6 snRNA phosphodiesterase, acting as an exoribonuclease [36]. Some of these abnormalities, known as radial ray malformations, affect development of bones of the forearms and the thumbs. Of note, patients have neutropenia that associates this syndrome with defects in hematopoiesis. Underdevelopment or absence of the bones of the forearms and the thumbs also occurs in the **Rapadilino syndrome** (Table 1), due to *RECQL4* gene mutation as well [37] (Table 2).

Cartilage-hair hypoplasia presents with dwarfism, hypotrichosis and immune deficiency with recurrent infections (Table 1). Long bones show metaphyseal chondrodysplasia. Patients show unusual flexibility of some joints, but difficulty in elbow full extension. Hairs are thin and hypopigmented because of the absence of their cores. They also show skin hypopigmentation, nails and dental malformations [38]. Furthermore, cartilage-hair hypoplasia induces immune failure, with severe forms classified as combined immunodeficiency (SCID) as they lack immune response against bacteria, viruses, and fungi and are prone to develop sepsis, while mild immune deficiency causes infections of the respiratory system, ears, and sinuses [39]. Paradoxically, some patients show autoimmune disorders [40]. Affected individuals are also prone to develop skin basal cell carcinoma, leukemia and lymphoma. Additional symptoms are gastrointestinal disorder with inability to absorb nutrients, celiac manifestations, severe constipation, enlarged colon, anal stenosis or esophageal atresia [38].

Cartilage-hair hypoplasia is caused by mutations in the *RMRP* gene encoding the noncoding RNA of the mitochondrial RNA-processing endoribonuclease, or RNase MRP (Table 2). The function of this enzymatic complex is in the replication of mitochondrial DNA and probably also in the processing of mitochondrial ribosomal RNA and in the control of the cell cycle. *RMRP* mutations cause noncoding RNA instability and inability to bind proteins of the RNase MRP enzyme complex. Cartilage-hair hypoplasia has an autosomal recessive inheritance [38].

Thrombocytopenia with absent radii is another syndrome with hematopoietic failures and skeletal anomalies [41] (Table 1). The condition has an autosomal dominant inheritance pattern and presents with hypomegakariocytic thrombocytopenia and bilateral radius aplasia [42] as well as gastrointestinal and cardiac anomalies [41]. The genetic abnormality is caused by a combination of a 1q21 microdeletion with a common single nucleotide polymorphism on the remaining allele of the *RBM8A* gene encoding the RNA-binding motif protein 8A, involved in mRNA transport to the cytoplasm [43] (Table 2).

The **IVIC** syndrome (the name derives from the Institute in which it was described - Instituto Venezolano de Investigaciones Cientifica), also known as **oculo-oto-radial syndrome** [44,45], presents with radial ray hypoplasia (Table 1). It is an autosomal dominant disorder with wide penetrance. The mutant gene (*SALL4*) encodes a transcription factor that contributes to the maintenance and self-renewal of embryonic and hematopoietic stem cells [46,47] which explains the Fanconi anemia observed in patients (Table 2). IVIC syndrome shares an allelic disorder called **Okihiro** (or **Duane radial ray**) syndrome [45] (Tables 1, 2). Patients may also suffer from strabismus, hearing loss, imperforate anus and thrombocytopenia [44,45].

WT limb-blood syndrome (the acronym WT derives from the initials of the first family in which it was described) is also autosomal dominant (Table 1). Patients have Fanconi anemia and are at risk to develop leukemia and lymphoma [48]. This syndrome manifests radial-ulnar hypoplasia, bifid or hypoplastic thumbs and cutaneous syndactyly [48]. There is currently no information regarding the genetic defect and molecular dysfunction of WT syndrome.

Diamond-Blackfan anemia features low bone mineral density (BMD) of the spine and femoral neck in adults and children and presents with forearm anomalies [18] (Table 1). Patients may suffer from flatness of the palms (thenar eminences) and decreased radial pulsations [49]. They have short stature, malformed or absent thumbs and craniofacial anomalies. Renal and cardiac abnormalities also occur [49]. Affected individuals may have congenital erythroid hypoplasia. The disorder may be sporadic, autosomal recessive, autosomal dominant or X-linked [58]. The gene mutated in 25% of patients encodes the ribosomal protein RPS19 [50] and 35–40% have a gene locus mapping to the long harm of chromosome 8 [51] (Table 2). **Aase-Smith syndrome** is characterized by triphalangeal thumbs [52] (Table 1). A subset of these patients has a variant of the Diamond-Blackfan anemia and carries a gene defect associated with synthesis of ribosomal proteins [49], while in approximately 45% of patients no genetic cause is known (Table 2).

Schwachman-Diamond syndrome is an autosomal recessive disease with a hallmark of neutropenia and exocrine pancreas insufficiency [53]. It is attended by low BMD and skeletal malformations [18] (Table 1). Most patients carry mutations of the *SBDS* gene that encodes the highly conserved ribosomal maturation protein, SBDS [54] (Table 2). The disorder manifests by methaphyseal dysostosis, especially of femurs, and marrow failure leading to cytopenia [53]. One third of patients develop myelodysplastic syndrome which may progress to leukemia, while a minority have short stature, craniofacial abnormalities and syndactyly [53].

Hereditary myeloproliferative disorder is an autosomal recessive disease also known as **agnogenic myeloid metaplasia** or **familial infantile myelofibrosis** [55] (Table 1). Patients present with fibrotic marrow causing failed hematopoiesis [56]. Therefore, ectopic hematopoiesis is observed in spleen and liver with leukoerythroblastosis and tear-drop cells (dacrocytes) [55,56]. Patients also have osteosclerosis of unknown etiology [1]. The etiology of the disorder is still unknown (Table 2).

Histiocytosis-lymphadenopathy plus syndrome includes diseases also known as Rosai-Dorfman and Faisalabad histiocytosis. They show mutations in the *SLC29A3* gene, which encodes the Equilibrative Nucleoside Transporter 3 (ENT3) localized in lysosomal and mitochondrial membranes [57] (Table 2). **Rosai-Dorfman disease**, was considered a non-hereditary condition (Table 1) but seven sibling pairs, including three sets of identical twins, have been reported with this syndrome. It is characterized by massive lymphadenopathy, polyclonal hypergammaglobulinemia and medullary bone solitary or multifocal lytic areas [58] which could be due to the inflammatory status of the patients [59]. **Faisalabad histiocytosis** is morphologically similar but clinically different, with autosomal recessive inheritance mapping to chromosome 11q25 [60] (Table 1). Patients have joint deformities and sensorineural hearing loss at birth. They develop short stature, generalized lymphadenopathy, polyclonal hypergammaglobulinemia and swelling of eyelids that contains histiocytes [60].

5. Congenital bone diseases with hematological failure

In 2015, 436 hereditary skeletal pathologies were described in a seminal nosology and classification report [61]. They were grouped in 42 categories based on their molecular, biochemical and (or) radiographic criteria. The causative mutations of 364 of these disorders associated with 226 genes are known [69]. In some of these syndromes, bone anomalies are associated with hematologic failure.

The **bent bone dysplasia syndrome** is a perinatal lethal skeletal disorder with bent long bones [62] (Table 1). Calvarial bones are poorly mineralized and patients have craniosynostosis and hypoplastic pubis and clavicles. Facial deformities also appear, including low-set ears, hypertelorism, midface hypoplasia, prematurely erupted fetal teeth

and micrognathia [62]. Autopsies of 4 fetuses with bent bone dysplasia revealed 1 with hepatosplenomegaly and extramedullary hematopoiesis [62] of unknown origin. There were small hypertrophic chondrocytes at the growth plate and a thick periosteum characterized by hypercellularity. Mutations of the *FGFR2* gene occurred (Table 2). They were heterozygous and consisted of missense nucleotide changes leading to the introduction of a polar amino-acid into the transmembrane helix of the FGFR2 receptor [62,63].

Osteogenesis imperfecta is a family of collagen mutation disorders with various patterns of inheritance (Table 1). Bones are fragile and break with low energy trauma [64]. Most patients have mutations of collagen 1α chains but other genes, associated with collagen metabolism, are affected in a minority of them [64] (Table 2). Patients suffer from a variety of other symptoms which classify osteogenesis imperfecta into at least 8 types [64]. The pattern of inheritance can be autosomal recessive or dominant with outcome that ranges from mild to severe. Common symptoms are short stature, multiple fractures, blue sclerae, loose joints, hearing loss, and problems with breath and teeth. Patients may also have artery dissections (generally in cervical artery and aorta) [64]. In a number of patients increased serum pyrophosphate and mild bleeding tendency occur with abnormal platelet aggregation and adhesion to collagen [65–67]. These defects are associated with impaired release of platelet factor 3 [66]. Coagulation problems also occur in other connective tissue disorders and may depend on altered energy metabolism [66]. Therefore, platelet dysfunction in osteogenesis imperfecta could be induced by impaired ATP/ADP metabolism rather than by a primary platelet alteration. In sporadic cases, a mild form of osteogenesis imperfecta occurs in patients affected by sickle cell disease [68] and anemia [69]. However, the molecular mechanisms associating these hematological conditions with collagen alterations are unknown.

6. Congenital hematologic anomalies affecting bone turnover

In 2006, Gurevitch and Slavin theorized that postmenopausal osteoporosis could have a hematological etiology given that women lose blood during menses, stimulating marrow expansion and resulting in increased myeloid cells, including osteoclast progenitors, thus accelerating bone resorption and bone loss [70]. This theory is however, challenged by the fact that hematopoietic tissue does not expand with age [71], although selective pressure towards certain lineages, including the monocyte/macrophage family, is theoretically possible.

An association between bone turnover and hematologic anomalies is clearly observed in several genetic disorders (Table 1). For instance, **Ghosal type hemato-diaphyseal dysplasia** [72] (Table 1) is caused by homozygous mutations of the *TBXAS1* gene, encoding the enzyme thromboxane synthase [73] (Table 2). Thromboxane synthase is highly expressed in platelets and converts arachidonic acid to thromboxane A2, also known as prostaglandin H2 [74]. Thromboxane A2 has prothrombotic properties, promoting platelet aggregations. Affected subjects suffer from diaphyseal dysplasia and refractory anemia. At variance with Camurati-Engelmanm disease, which affects only the diaphysis, in Ghosal type hemato-diaphyseal dysplasia the anomaly also appears in the metaphysis. As highlighted by its name, affected patients have severe pancytopenia. Medullary cavities of the long bones are enlarged, with cortical hyperostosis. Despite large cavities, the marrow is hypocellular. In Ghosal type hemato-diaphyseal dysplasia, anemia and marrow fibrosis are detected [72]. Surprisingly, no blood clotting defects are noted [72], suggesting compensation by other prothrombotic molecules may occur. However, in Ghosal type hemato-diaphyseal dysplasia, thromboxane A2 metabolism is altered resulting in an increase of other prostaglandins, including prostaglandin E2, known to be involved both in bone remodeling and erythropoiesis [75]. This dual role of prostaglandin E2 could explain the association of the bone anomaly with the hematologic failure [73]. Furthermore, thromboxane A2 regulates osteoblast expression of the *TNFSF11* and *TNFRSF11B* genes, encoding Receptor Activator of NF-κB Ligand (RANKL) and Osteoprotegerin (OPG), respectively [73]. Given the essential role of these two cytokines in bone resorption, alteration of this thromboxane A2-mediated mechanism could contribute to the bone phenotype observed in the disease.

Severe congenital neutropenia is characterized by recurrent infections (Table 1). Neutrophil deficiency is present already at birth or appears immediately after birth. Infants show infections of the sinuses, lungs and liver, fever, gingivitis and dermatitis [76]. This condition is associated with osteopenia at least in 40% of patients, which can then evolve towards overt osteoporosis. In most severe forms, osteoporosis appears already in infancy and worsens with age [77]. The diseases can also be associated with myelodysplastic syndrome or leukemia, seizures, growth retardation, heart and genital abnormalities [76].

The pattern or inheritance of severe congenital neutropenia is generally autosomal recessive, however X-linked pattern is also known [78]. Several genes can be involved in severe congenital neutropenia (Table 2). They play a role in the maturation and function of neutrophils, promoting cell survival and response to immune signals. Most patients (about 50%) harbor mutations of the *ELANE* gene [79], encoding the neutrophil elastase, a serine proteinase released by neutrophils and macrophages during inflammation, which destroys bacteria and host tissues [78]. About 10% of patients instead harbor mutations in the *HAX1* gene, encoding the HS-1-associated protein X-1 (HAX1), where HS-1 is a Src family tyrosine kinase substrate. HAX1 is a mitochondrial protein that regulates apoptosis [80]. HAX1 protein contributes to the activation of the Granulocyte Colony-Stimulating Factor (G-CSF) signaling pathway and could cause osteopenia enhancing bone resorption [81]. Various other genes, including *CSF3R*, *G6PC3*, *GFI1*, *JAGN1*, *TCIRG1*, *VPS45* and *WAS* (Table 1) account for a small portion of patients, while about 30% of them have unknown genetic defects, with some cases with no familial history, thus classified as sporadic [81]. Interestingly *GFI1* encodes a transcription factor that control HSC quiescence [82] and osteoblast differentiation inducing epigenetic changes in the *RUNX2* promoter [83].

Anemia is a hallmark of several genetic diseases caused by failures in erythropoiesis, often associated with other cellular deficiencies within marrow. These genetic conditions may have skeletal consequences, including changes in bone mass and malformations.

Thalassemia is a primary, autosomal recessive defect of erythrocytes due to mutations of hemoglobin α or β preventing oxygen transport [84] (Table 2). The disease manifests with severe anemia [84] (Table 1). This condition is often associated with skeletal abnormalities [85]. Transfusions and treatment with iron chelators to prevent iron overload are important modes of therapy [86]. Given the essential role played by oxygen in all tissues, thalassemia affects all organs, creating hormonal deficiency and increasing bone turnover [87,88]. Decreased bone mass appears in thalassemic children and prevalence increases due to longer life expectancy [89–92]. Hypogonadotropic hypogonadism and delayed puberty, deficiency of growth hormone and IGF-1, renal insufficiency and iron toxicity are among the causes of bone loss in thalassemia [89–92]. Affected individuals may exhibit RANKL/OPG imbalance that favors bone resorption. Other common endocrine abnormalities include hypoparathyroidism, vitamin D deficiency, hypothyroidism and diabetes [92], which can prevent the achievement of the normal peak bone mass. Osteopenia and osteoporosis affect at least 50% of patients and are treated with antiresorptive drugs [90].

Similar to thalassemia, **sickle cell disease** is an autosomal recessive disorder due to hemoglobin anomalies causing severe anemia (Table 1). Mutations of β-globin produce hemoglobin S which replaces one or both β-globins in the hemoglobin complex [93,94] (Table 2). This altered form of β-globin distorts the shape of the erythrocytes which assume a sickle-like appearance. Sickle erythrocytes have short life span and are rigid, often attaching to endothelium and disturbing blood flow [93,94]. In fact, major features of sickle cell disease are hemolytic anemia and vaso-occlusive syndrome, causing tissue injury [93,94]

eventuating in skeletal abnormalities such as osteonecrosis and osteomyelitis [89,95,96]. Vitamin D deficiency is common in sickle cell disease [96] and patients present with high rates of osteopenia and osteoporosis [1,89].

7. Congenital bone diseases affecting osteoclasts and hematopoiesis

Hematopoiesis is a regulated and complex event involving interactions between hematopoietic stem (HSC) and bone cells. A subset of osteoblasts contributes to the so-called endosteal niche that maintains HSC quiescence, eventuating in a long-term reservoir of these cells thereby preventing progenitor exhaustion [97]. Blood vessels also regulate hematopoiesis through a series of cellular communications that govern exit of HSCs from quiescence and expansion of myeloid lineages [98] (Fig. 3). Less known, but probably equally important, is the role of osteoclasts in the regulation of hematopoiesis [99]. Insights into the role of osteoclasts, albeit presently limited, may provide new prospective for understanding the interaction between bone and blood. An obvious role of osteoclasts in creating the conditions for normal hematopoiesis is through their primary function in bone resorption. By removing bone matrix during accrual, osteoclasts make room to lodge marrow. Consequently, impairment of osteoclast activity will prevent the physiologic development of hematopoiesis (see below) (Fig. 2).

Besides this "physical" consequence of osteoclast function that is essential for creating marrow space, osteoclast enzymatic activity may play a more direct role on myelopoiesis by regulating HSC-niche interaction and HSC mobilization [99,100]. For instance, the enzyme necessary for the bone collagen degradation during resorption, cathepsin K, cleaves also SDF-1, a chemokine that contributes to the anchorage of HSCs to the quiescence niche [101]. Breakdown of SDF-1 mobilizes HSCs and may increase release of immature myeloid progenitors into the circulation [101,102]. Another enzyme highly expressed by osteoclasts is metalloproteinase 9 (MMP-9), which recruits immature myeloid progenitors by CXCR4 dependent mechanism stimulated by RANKL and inhibited by calcitonin, an anti-osteoclastic hormone [103]. MMP-9 is also implicated in release of the c-kit ligand, which induces the switch of HSCs from quiescent to proliferating status [86]. Another possible role for MMP-9 is HSC mobilization induced by two chemokines, GRO/β/CXCL2 and GROβ$_T$/CXCL2$_{\Delta 4}$ [104]. This posture is challenged, however, by the fact that the MMP-9 deleted mice have no impairment of hematopoiesis [105].

Another means by which osteoclasts could contribute to hematopoiesis is through the release of calcium during bone resorption (Fig. 3). In this regard, HSC engraftment at the endosteal niche is an event requiring activation of the calcium-sensing receptor and deficiency in calcium signaling induces mobilization of immature progenitors [106].

The fact that G-CSF increases osteoclast activity favors the concept that resorptive polykaryons regulate hematopoiesis [107]. This occurrence is paralleled by cleavage of SDF-1 in marrow [101] which, as stated above, plays a role in the mobilization of immature progenitors into the circulation [102]. On the other hand, SDF-1 also contributes to osteoclast differentiation [108]. It is therefore likely that G-GSF and SDF-1, in partnership, regulate hematopoiesis and bone resorption.

Osteopetrosis (or marble bone disease) is a family of genetic disorders characterized by arrested osteoclast formation or dysfunction of the differentiated cell [109,110] (Table 1). Regardless of genetic basis (Table 2), osteopetrosis increases bone mass. The failure to replace old, effete bone with new healthy bone causes skeletal fragility and predisposition to low impact fractures. Osteopetrotic infants are generally anemic and susceptible to infections, which may mistakenly suggest a purely hematological disease. Osteopetrosis, however, is easily diagnosed radiographically due to high bone density and the so-called "bone-in-bone" appearance (denser marginal areas of mineralization, intermediate less dense areas and innermost denser areas), the narrowing of the bone marrow space and the appearance of alternating lucent areas in the metaphyseal regions [109,110]. Impairment of bone marrow development is due to insufficient space, a primary consequence of the lack of resorption, although marrow fibrosis is often profound (Fig. 2). The reduction of bone marrow space eventuates in extramedullary hematopoiesis especially in liver and spleen [109]. However, in the light of evidence of a direct role of osteoclasts in regulation of the HSC pool and osteoblast recruitment, it is possible that the resorptive cell may affect the HSC niche located at the endosteal surface [106]. In fact, osteopetrotic oc/oc mice have reduced HSC numbers and downregulation of HSC-specific genes [111]. Furthermore, they have defective mesenchymal stem and progenitor cells, fail to effectively reconstitute hematopoietic stem and progenitor cells and exhibit resistance of mesenchymal stem and progenitor cells to G-CSF [112]. These observations suggest the involvement of osteoclasts in marrow niche homeostasis causing imbalance of hematopoiesis when they are dysfunctional [112]. More circulating hematopoietic stem and progenitor cells are observed not only in mice but also in osteopetrotic humans. There is, however, a large heterogeneity in both species that compromises any conclusion regarding the universality of the mechanisms involved.

Osteopetrotic patients may present with high numbers of nonfunctional osteoclasts due to mutations of genes implicated in the mechanism of bone resorption, such as *TCIRG1, CLCN-7, OSTM1 SNX10, PLEKHMI,* and *CAII* (osteoclast rich) (Table 2). Alternatively, they may lack osteoclasts due to mutations of genes implicated in the process of osteoclast formation, such as *TNFSF11* and *TNFRSF11A* encoding RANKL and RANK, respectively (osteoclast poor) [113] (Table 2). The distinction between osteoclast-rich and -poor osteopetrosis is clinically

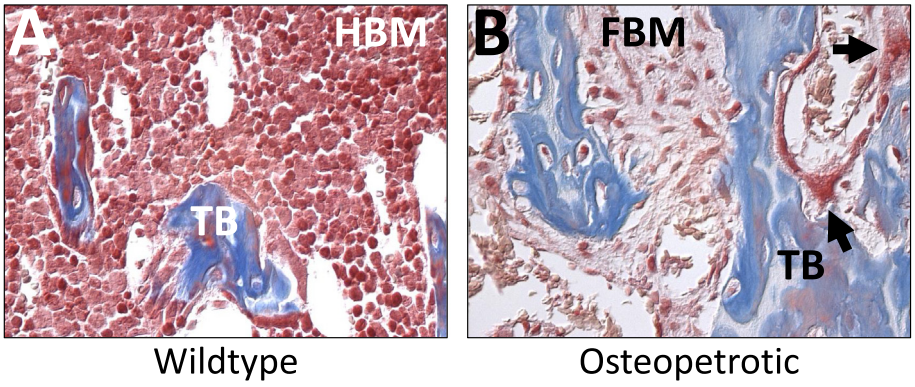

Fig. 2. Hematopoietic and fibrotic bone marrow. Histological sections of mouse tibias from a wildype and an osteoclast-rich osteopetrotic mouse carrying a homozygous *Clcn7*^{G213R} knock-in mutation showing (A) the wildtype hematopoietic bone marrow (HBM) and (B) the osteopetrotic fibrotic bone marrow (FBM). TB: trabecular bone; arrows: osteoclasts. Original magnification 40×.

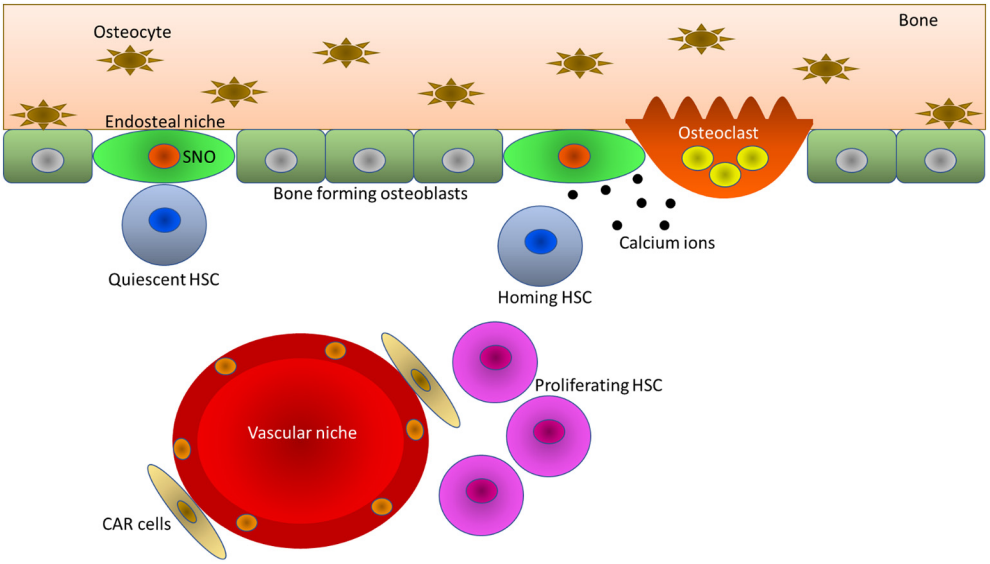

Fig. 3. Hematopoietic cellular niches. Cartoon illustrating the cellular niches involved in hematopoiesis. The osteoblast niche, made up by Spindle-shaped N-cadherin positive Osteoblasts (SNOs), recruits HSCs inducing their long-term quiescence. HSC homing to the endosteal niche is favored by the microenvironmental high calcium concentration caused by bone resorption. Mobilization of HSCs from the endosteal niche and their recruitment to the vascular niche, made up by sinusoidal vasculature and adjacent CXCL12-abundant reticular (CAR) cells, induce HSC proliferation and progression towards lineage-specific progenitor cells.

important as the former, but not all the latter patients may be candidates for curative marrow transplantation.

In the presence of dysfunctional osteoclasts, the marrow space is intensely fibrotic (Fig. 2), while in the absence of osteoclasts it appears severely reduced but with no fibrosis [114]. Interestingly, RNA deep sequencing of osteopetrotic osteoclasts, affected by a heterozygous missense mutation of the *CLCN-7* gene encoding for the chloride/proton antiporter type 7, shows upregulation of a series of pro-fibrotic genes (unpublished results). This observation suggests that impairment of bone resorption is somehow associated with the alteration of collagen synthesis in marrow stroma, adding additional information to the complex crosstalk between osteoclasts and hematopoiesis.

8. Future development and clinical impact

It is now several years that the interaction between bone and blood is being investigated and this effort produced relevant new knowledge with a clinical impact. For instance, the recognition of the hematological origin of osteoclasts [115] has led to the clinical procedure of bone marrow transplantation that is curative in severe osteopetrosis [116]. The in-depth phenotyping of bone diseases has led to the identification of previously unrecognized marrow failures and genetic studies have demonstrated that molecular alterations are shared by blood and bone cells, thus facilitating the diagnosis and the subsequent treatments when they are feasible. The deep understanding of the cellular and molecular relationships between marrow and bone should represent important future goals of the biomedical research, and we can predict that the new knowledge recently accumulated in the hematopoietic and mesenchymal stem cell field, along with the molecular definition of the marrow stem cell niches, represent the foundation for future studies that will increase the clinical impact of the discoveries. Ultimate goals of research should be the early and precise diagnosis followed by healing treatments that should not be only palliative. The way is paved by the recent clinical results obtained by gene therapy [117], considered until recently the “mission impossible” of biomedical and clinical research, and the hope for the future is the development of effective and safe gene editing procedures [118], pioneered the CRISPR/Cas9 methodology that is just now being investigated for potential clinical application [119]. It is a long way to go, but science progresses gradually and what appears impossible now will be routinely applied in the future.

9. Conclusions

In this article, we made an “excursion” to clarify the interactions between congenital bone diseases and blood. We highlighted that this crosstalk is two-way and that a number of genes are implicated in the processes of hematopoietic cell generation and skeletal development. Disruption of these mechanisms causes marrow failure and skeletal malformations. On the other hand, certain congenital hematological diseases imbalance bone remodeling and reduce bone mass inducing secondary osteoporosis Alternatively, osteoclast diseases may reduce the space for bone marrow formation and affect the HSC niche and mobilization of HSCs and progenitors into the circulation. We conclude that, although the underlying mechanisms have not yet been fully elucidated, the data available indicate the existence of intricate communication between bone and blood that is disrupted by a series of congenital conditions that ultimately affect both tissues. Understanding the pathophysiology of the congenital bone-blood diseases could facilitate diagnosis and improve therapy of patients.

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