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SCLEROSING BONE DYSPLASIAS: LEADS TOWARDS NOVEL OSTEOPOROSIS

TREATMENTS

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ABSTRACT

Sclerosing bone dysplasias are a group of rare, monogenic disorders characterized by increased bone density resulting from the disturbance in the fragile equilibrium between bone formation and resorption. Over the last decade major contributions have been made towards better understanding of the pathogenesis of these conditions. These studies provided us with important insights into the bone biology and yielded the identification of numerous drug targets for the prevention and treatment of osteoporosis. Here, we review this heterogeneous group of disorders focusing on their utility in the development of novel osteoporosis therapies.

1 INTRODUCTION

The strength and shape of the skeletal bones are sustained by the fine balance between bone formation and resorption. Disruptions of this equilibrium may lead to pathologies characterized by abnormally increased or reduced bone mineral density (BMD). From these pathologies osteoporosis emerges as the heaviest socioeconomic burden on our population [1]. Based on the combination of its high prevalence and the high heritability of relevant skeletal features, estimated at 25-85% percent, it is clear that genetic studies can highlight relevant, biological mechanisms that could be targeted for the pharmacological treatment of this complex and multifactorial condition [2]. However, with the scarcity of suitable, monogenic disease models for low BMD, comprising only osteoporosis pseudoglioma syndrome and some forms of osteogenesis imperfecta, scientific attention shifted towards investigation of disorders residing on the other side of the spectrum. **Sclerosing bone dysplasias** are a group of rare, monogenic disorders characterized by pathological increase in bone density resulting in a broad set of radiological and clinical abnormalities. These diseases are caused by a diverse spectrum of genetic factors. Over the years, studies unraveling these pathogenic mechanisms provided major contributions towards the better understanding of bone biology. Interestingly, some of the genes identified this way represented promising targets for the development of novel treatments for osteoporosis. In this review we summarize the major sclerosing bone dysplasias and discuss the lessons learned from the study of these rare disorders that contributed to current line of osteoporosis management.

2 BONE DISORDERS WITH INCREASED BMD

	Disease	Form	Genes	Mutation	Function	Radiological features
Decreased bone resorption	Osteopetrosis	X-linked	IKBK	hypomorphic	OC differentiation	Optional bone thickening
		ARO	TNFSF11 TNFSF11A CAII TCIRG1 CLCN7 OSTM1	loss of function loss of function loss of function loss of function loss of function	OC differentiation OC differentiation Acidification by OC Acidification by OC Acidification by OC Acidification by OC	General ↑bone density, sclerosis at cranial base, "Erlenmeyer flask" deformity of bones, loss of trabecular structure, poor definition between cortex and medulla
		IARO	PLEKHM1 CLCN7 SNX10	loss of function hypomorphic loss of function	Acidification by OC Acidification by OC Acidification by OC	General sclerosis of the skeleton, widened metaphyses
		ADO	CLCN7	dominant negative	Acidification by OC	General sclerosis predominantly at vertebral endplates, iliac wings and the skull base
	Pycnodysostosis	AR	CTSK	loss of function	Collagenase activity	General sclerosis, short stature, dolichocephaly, open fontanel, clavicular dysplasia, obtuse angle of the mandible, short terminal phalanges
Increased bone formation	High bone mass phenotype	AD	LRP5	gain of function	Wnt signaling coreceptor	↑bone density, cortical hyperostosis at cranium, mandible and tubular bones
	Sclerosteosis	AR	SOST LRP4	loss of function loss of function	Wnt signaling inhibitor	Hyperostosis at calvaria, skull base, mandible and tubular bones; syndactyly, tall stature
	Van Buchem disease	AR	SOST	52kB deletion suppressing SOST expression	Wnt signaling inhibitor	Hyperostosis at calvaria, skull base, mandible
	Craniodiaphyseal dysplasia	AD	SOST	loss of function	Wnt signaling inhibitor	Facial distortion, hyperostosis and sclerosis of cranial bones ("leontiasis ossea")
	Osteopathia striata (with cranial sclerosis)	X-linked	WTX	loss of function	Wnt signaling inhibitor	Metaphyseal striations, sclerosis at the skull base, absent fibulae
	Cranio-metaphyseal dysplasia	AD and AR	ANKH GJA1	loss of function (not yet known)	OB differentiation (not yet known)	Facial distortion, hyperostosis and sclerosis of cranial bones
	Camurati-Engelmann disease	AD	TGFβ1	gain of function	OB differentiation/proliferation	Cortical thickening, sclerosis of the diaphysis of the long bones by endosteal and periosteal proliferation, sclerosis of the basilar portions of the skull
	Osteopoikilosis/Buschke-Ollendorff syndrome	AD	LEMD3	loss of function	TGFβ and BMP signaling inhibitor	"Spotted bone"- small ovoid or lanceolate sclerotic lesions,
	Raine syndrome	AR	FAM20C	loss of function	OB differentiation	Severe facial distortion, generalized bone sclerosis
Increased bone turnover	Paget's disease of bone	AD	SQSTM1 VCP	gain of function	OC function	Focal abnormalities at one or multiple skeletal sites, bone deformities,
	Osteoectasia with hyperphosphatasia (Juvenile Paget's)	R	TNFRSF11B	loss of function	OC function	"Bowling" bones, short stature, kyphoscoliosis
	Familial expansile osteolysis	AD	TNFRSF11A	gain of function	OC function	Focal lesions, extreme bone deformities
	Expansile Skeletal Hyperphosphatasia	AD	TNFRSF11A	gain of function	OC function	Focal lesions, bone deformities

Table 1: Summary of main sclerosing bone dysplasias including mode of inheritance, causative genes, type of mutations identified in given genes, functions of causative genes and radiological hallmarks of the disorders; **ARO** (autosomal recessive osteopetrosis), **IARO** (intermediate autosomal recessive osteopetrosis), **ADO** (autosomal dominant osteopetrosis), **AR** (autosomal recessive), **AD** (autosomal dominant), **OC** (osteoclast), **OB** (osteoblast); Gene names were explained in the text.

2.1 SCLEROSING BONE DYSPLASIAS CAUSED BY DECREASED BONE RESORPTION

One possible cause of elevated BMD is the impairment of bone resorption. As nicely demonstrated by the heterogeneous group of **Osteopetroses**, this can be due to impaired osteoclast differentiation or function. Two major modes of inheritance have been described for these conditions: autosomal recessive in case of severe forms, and autosomal dominant, usually leading to relatively mild forms. **Autosomal Recessive Osteopetrosis (ARO)** is often diagnosed shortly after birth and is characterized by a general increase of BMD, “Erlenmeyer flask” shape bones that display loss of trabecular structure and bone marrow failure due to the reduced bone marrow space. Neurological complications occur due to sclerotic changes at cranial foramina. The thorax is often small and sometimes hypertelorism, exophthalmos and micrognathia are observed. Increased propensity to fractures is a consequence of brittle bone structure. ARO is predominantly (~50% of cases) caused by mutations in *TCIRG1* encoding for a subunit of vacuolar H⁺-ATPase that transports protons into the resorption lacuna during the process of acidification of this compartment [3, 4]. Around 15% of ARO cases are caused by loss of function mutations in the *CLCN7* gene encoding the chloride channel crucial for the maintenance of the electric charge on both sides of the ruffled border [5]. Deactivating mutations in another subunit of this protein complex, namely *OSTM1*, give rise to up to 6% of ARO [6]. Another rare cause of ARO is a loss of function mutation in the gene encoding carbonic anhydrase II (*CAII*) that hinders the intracellular production of protons required for acidification of resorption lacuna [7].

In a subset of cases a reduction in the number of osteoclasts is observed causing a relatively slower disease progression and milder clinical manifestation. These, so called, **osteoclast poor forms of osteopetrosis** arise mainly from mutations in *TNFSF11* and *TNFSF11A* coding for receptor activator of NF-κB ligand and its receptor respectively [8, 9]. Disruption of this pathway leads to impairment of osteoclast activation and differentiation. Hypomorphic mutations in this pathway (the inhibitor of nuclear factor kappa-B kinase subunit gamma – *IKBKG*) also lead to an X-linked form of osteopetrosis, namely **anhidrotic ectodermal dysplasia and immunodeficiency**. [10]. A less severe clinical picture is also observed in the **intermediate autosomal recessive form (IARO)**. Short stature, delayed dentition and increased fracture risk are not accompanied by severe symptoms nor neurological complications. It has been shown that these forms of osteopetrosis are caused

by hypomorphic mutations in *CLCN7* and loss of function mutations in *PLEKHM1* [11]. In addition, missense mutations in *SNX10*, coding for sorting nexin 10 protein which is crucial for endosomal trafficking within the osteoclast have been identified in patients suffering from IARO [12].

The **autosomal dominant form of osteopetrosis (ADO)** can also result from mutations in *CLCN7* but it is believed that in these patients functional complexes of a mature chloride channel are formed from both normal and mutant proteins resulting in only partial disruption of ion transport [13]. Recently a number of patients diagnosed with **ADO (type 1)** were shown to carry mutations in *LRP5* gene, a coreceptor of Wnt-signaling. Therefore, this condition is no longer considered part of the group of the osteopetroses as being caused by increased bone formation [14].

Mutations in the main cysteine protease of the osteoclast- Cathepsin K compromise collagenase activity of the cell and result in **Pycnodysostosis**- a rare, autosomal recessive disorder. Patients display short stature, open fontanel, clavicular dysplasia in addition to generally elevated bone density and risk of fracture. The osteocytes in patients suffering from this disease appear normal, however intracellular depositions of undegraded collagen are observed due to the lack of relevant enzymatic activity [15].

2.2 SCLEROSING BONE DYSPLASIAS CAUSED BY ENHANCED BONE FORMATION

Sclerosing bone dysplasias may also result from increased osteoblastic activity. Autosomal dominant **High bone mass phenotype (HBM)** is a mild example of such disorder with patients presenting with elevated BMD, cortical thickening in cranial and tubular bones and resistance to fractures. It has been shown that the disorder is caused by activating mutations in the *LRP5* gene serving as a coreceptor for Wnt signaling [16, 17]. The role of this pathway in bone biology was also elucidated by the discovery of loss of function mutations in the same gene causing Osteoporosis Pseudoglioma Syndrome characterized by early onset osteoporosis [18]. These results highlight Wnt signaling as one of the key players in osteoblastic differentiation, activation and survival. **Sclerosteosis** originates from loss of function mutations in the gene encoding sclerostin, a potent Wnt signaling inhibitor [19, 20]. Sclerosteosis patients present with tall stature, syndactyly and generalized sclerosis of the skeleton, especially the skull bones and mandible. Some patients suffer from neurological complications such as cranial nerve palsies due to the sclerosis of the skull base or cephalgia caused by increased intracranial pressure. In 2011, we demonstrated that mutations in another Wnt-signaling coreceptor, namely *LRP4*, can also cause sclerosteosis [21]. *LRP4*, has been shown to facilitate sclerostin inhibitory action and therefore partial loss of function mutations in this gene result in a similar

phenotype as the mutations in *SOST*. A related, yet milder condition, is **Van Buchem Disease (VBD)**. Patients suffering from this rare, autosomal recessive disorder display sclerosis of the skeleton, most prominent in the skull bones, and show progressive enlargement of the mandible. The disease is caused by a 52kb deletion of a regulatory element localized 35kb downstream from the *SOST* gene, resulting in decreased production of sclerostin [22]. Recently, mutations in *SOST* gene have also been described as causative for **craniodiaphyseal dysplasia**, a severe disorder marked by typical facial distortion termed “leontiasis ossea”. These mutations have been shown to largely impair sclerostin secretion [23].

Osteopathia striata is another sclerosing bone disorder, however with X-linked dominant mode of inheritance. This disease usually results in fetal or neonatal death in males, while females display longitudinal striations in the submetaphyseal regions of long tubular bones, pelvis and scapula. Clinical findings include cleft palate, hearing loss and macrocephaly. Causative mutations have been found in the *WTX* gene encoding a Wnt-signaling inhibitory protein capable of binding β -catenin [24]. The phenotypic variability amongst affected females is most likely due to non-random X-inactivation.

Individuals with **Cranio-metaphyseal dysplasia** usually show a peculiar face with hypertelorism and a thick bony wedge over the bridge of the nose and glabella. Narrowing of the nasal passages may result in mouth breathing. Frequently, signs of cranial nerve impingement are seen with hearing loss, impaired vision or facial paresis. Mutations in the *ANKH* gene encoding a membrane transporter of pyrophosphate have been shown to cause the milder and more common autosomal dominant form of the disease [25, 26]. Pyrophosphate is believed to inhibit mineralization of the bone matrix; therefore mutations in the gene might impair the transporter role of ANKH. Moreover, ANKH has also been shown to stimulate osteoblastic maturation and differentiation. Recently, mutations in the *GJA1* gene, encoding connexin 43, have been identified in patients suffering from the autosomal recessive form of the disease [27].

Camurati-Engelmann disease is a rare, autosomal dominant condition characterized by muscular weakness and leg pain in affected individuals. Moreover, cortical thickening of the long bones and hyperostosis of the skull base is observed. Camurati-Engelmann disease is caused by activating mutations in *TGF β 1*. Normally, TGF β 1 is stored in the bone in an inactive form due to its binding with latency-associated protein (LAP) [28, 29]. Resorbing osteoclast releases the complex from the bone tissue initiating the migration of mesenchymal stem cells and their differentiation towards osteoblasts. With mutations disrupting the binding between TGF β 1 protein and LAP, this controlling process is disabled which may lead to pathologically up-regulated bone formation.

Mutations in *LEMD3*, a nuclear membrane protein that antagonizes both the TGF β and BMP signaling pathways, have been identified as causative for **Osteopoikilosis** [30, 31]. This autosomal dominant skeletal dysplasia is largely asymptomatic with radiological features including small, focal lesions at one or multiple skeletal sites. If the bone phenotype is accompanied by connective tissue nevi or juvenile elastoma, the condition is referred to as the **Buschke-Ollendorff syndrome**.

Another disease caused by enhanced bone formation is **Raine syndrome**. This rare, severe syndrome usually results in death within the first weeks of life (mainly due to choanal atresia/stenosis). Surviving patients suffer from generalized increase in BMD, especially prominent at skull bones and severe facial distortion. Mutations in *FAM20C* gene encoding for a Golgi caseins kinase protein have been identified in patients with this disorder [32]. The protein has been shown to be crucial in the differentiation process of osteoblasts [33].

2.3 SCLEROSING BONE DYSPLASIAS WITH INCREASED BONE TURNOVER

As bone resorption remains tightly coupled with bone formation some disorders display elevated levels of both processes. Such is the case in **Paget's disease of bone (PDB)** where defective, numerous osteoclasts are accompanied by elevated osteoblastic activity. As a result of that, disorganized and weak bone tissue is produced. The typical age of disease onset situates within the 5th or 6th decade of life. Patients suffer from focal lesions affecting one or more skeletal sites, bone pain, increased incidence of fractures, bone deformities and elevated risk of developing osteosarcoma [34]. So far, mutations in *SQSTM1* (sequestosome 1) and *VCP* (valosin containing protein) have been discovered in PDB patients suggesting the possible involvement of autophagy in the pathogenesis of the disease [35-37].

Another example of disease with disturbed bone turnover is **Juvenile Paget's disease (Osteoectasia with hyperphosphatasia)** marked by severe malformations of the skeleton with "bowing bones", short stature and kyphoscoliosis. Inactivating mutations in *TNFRSF11B*, coding for osteoprotegerin (OPG) have been identified in this disease [38]. Activating mutations in *TNFRSF11A* coding for RANK have been identified in a rare autosomal dominant disorder named **Familial expansile osteolysis** resulting in the same pathogenic mechanism [39]. First hallmarks of the disease include hearing impairment and premature loss of dentition. Focal lesions, severe bone deformities, bone pain and frequent fractures appear early in life, usually between 15 and 45 years of age. In addition to that mutations in the gene encoding RANK have been found to be causative for **Expansile skeletal hyperphosphatasia** [40]. The disease is characterized by a progressive, generalized hyperostosis, early onset deafness and loss of dentition. Extreme bone pain usually occurs around adolescence affecting mainly the hands [41].

2.4 SCLEROSING BONE DYSPLASIAS WITH UNKNOWN GENETIC CAUSE

Although many genes involved in the development of sclerosing bone disorders are already discovered as demonstrated above, there are also a number of patients diagnosed with sclerosing bone disorders with unknown genetic cause. This group includes both patients with a clear-cut diagnosis but without a mutation in the causative genes as well as patients with disorders for which the responsible gene is yet to be determined. As examples of the former, there are still several cases diagnosed with sclerosteosis, high bone mass phenotype, endosteal hyperostosis or different forms of osteopetrosis without mutations in the known genes (Table 1) [42-44]. This can be due to locus heterogeneity or to misdiagnosis, as described recently for some cases of osteopetrosis by Pangrazio and colleagues [44]. On the other hand there are still several sclerosing bone disorders for which no causative genes are known despite some attempts to identify mutations. Fortunately, novel technologies like next generation sequencing will help with the identification of the causative genes in the yet molecularly unsolved bone dysplasias.

Next generation sequencing technologies have already proven to be successful in the gene discovery of many skeletal dysplasias which is nicely reviewed by Lazarus et al [45].

Hyperostosis cranialis interna is a rare autosomal dominant disorder which is characterized by intracranial hyperostosis and osteosclerosis of the skull. Linkage analysis in one Dutch family demonstrated recently that the causative gene is located in a region on chromosome 8p21 encompassing 64 genes, however the causative mutation is still to be identified [46]. **X-linked calvarial hyperostosis** is a very rare sclerosing bone disorders only affecting the skull. Only one family is described so far by Pagon and colleagues in 1986 but the causative gene is yet to be identified [47, 48]. Another sclerosing bone dysplasia with unknown cause is **melorheostosis**. It is characterized by asymmetric hyperostotic lesions in the cortex of tubular bones. The lesions usually affect one limb and besides the bone also other adjacent tissues can be affected [30]. Melorheostosis is, albeit rarely seen in families with osteopoikilosis and consequently, it was suggested that germline or somatic mutations in LEMD3 can be the cause for this disorder, however, several studies were unable to confirm this [30, 31, 49]. Finally, identification of the genetic cause of above described disorders and several other unidentified disorders such as for example **Pyle disease** and **osteomesopyknosis** will increase the insights in bone biology greatly which is interesting for the development of novel agents for treatment of common bone disorders such as osteoporosis [50, 51].

3 TARGETS FOR OSTEOPOROSIS TREATMENT

As mentioned before, osteoporosis is a common disease with a high socioeconomic impact. Nowadays, bisphosphonates are widely used for osteoporosis treatment. Bisphosphonates can

bind to bone and after internalization by the osteoclasts, they are able to prevent further bone resorption and bone loss. However, prevention of bone loss is shown to be insufficient for the prevention of osteoporosis related fractures. Genetic studies identifying the cause of monogenic sclerosing bone dysplasias have not only provided major insights into the bone biology, but also have highlighted novel pathways and sites of potential pharmacological intervention. Over the years a list of such findings has been translated into therapeutic strategies for management of osteoporosis (Table 2).

3.1 Inhibition of bone resorption

Identification of the genetic cause of osteopetrosis increased the insights into osteoclastogenesis and osteoclast function. In this way the RANK-RANKL-OPG pathway has been described as an important regulator of osteoclast formation and function. Binding between RANK and **RANKL** leads to osteoclast activation and is regulated by osteoprotegerin (OPG), an inhibitor of the pathway secreted by osteoblasts (Figure 1). Denosumab is a monoclonal humanized RANKL antibody mimicking the action of OPG and in this way preventing bone loss. Initially denosumab was approved by the FDA in 2010 for the treatment of postmenopausal osteoporosis. More recently, it is also approved for treatment in men with high risk of fracture [52]. Finally, a combined treatment with denosumab and teriparatide was recently evaluated in a two-year randomized trial in osteoporotic women. This combined therapy seems promising and showed a significant increase in spine, femoral neck and hip BMD in comparison to the use of a single therapeutic agent [53].

CLCN7 is another target for osteoporosis treatment that is identified through the study of causative genes for osteopetrosis. CLCN7 is a chloride channel present in the osteoclasts and important for acidification of the resorption lacunae. In 2004, NS3736 was identified as possible drug for osteoporosis treatment by inhibiting the osteoclastic chloride channel encoded by *CLCN7*. In ovariectomized rats, it was shown that NS3736 inhibits bone resorption without affecting bone formation [54]. However, further studies are needed to evaluate efficacy and safety of this small molecule. In addition to mutations in *CLCN7*, mutations in ***TCIRG1*** are also shown to be causative for autosomal recessive osteopetrosis. Furthermore, *TCIRG1* encodes a subunit of the osteoclast specific vacuolar H⁺-ATPase which is important for acidification of the resorption lacunae. Several inhibitors of the V-ATPase activity are described for example Bafilomycin A1, Concanamycin A, SB242784, FR167356 and FR202126, however, the available experimental data regarding treatment of osteoporosis for all components is limited and more research is needed regarding specificity, efficacy and safety [55].

Pycnodysostosis is another sclerosing bone disorder caused by defects in osteoclast function. Nonsense mutations in ***CTSK***, a lysosomal protease released by the osteoclast, are shown to be causative for the increase in bone mass seen in these patients [15]. The role of cathepsin K was

also confirmed by the osteopetrotic phenotype of the *ctsk* knockout mouse [56]. Based on these data, cathepsin K was considered as an interesting target for osteoporosis treatment. As a consequence, several inhibitors were developed but clinical trials for most agents are stopped as a result of adverse reactions or lack of selectivity. The most promising inhibitors which are still under study are Odanacatib, ONO-5334 and MIV-711 [57]. Clinical studies investigating the effect of Odanacatib on BMD are most advanced and have reached phase III. Results of the phase II clinical trials show that Odanacatib reduces bone resorption by blocking osteoclast function without affecting differentiation or survival. Finally, Odanacatib does not affect bone formation indicating that bone resorption and formation are uncoupled [58]. Although Odanacatib treatment looks promising, more studies are needed to determine its effect on fracture risk and safety [59].

3.2 Increasing bone formation

The importance of Wnt signaling in the regulation of bone formation was highlighted by genetic studies unraveling the genetic cause of the high bone mass phenotype, sclerosteosis and Van Buchem disease. Loss of function of **sclerostin** causes both sclerosteosis and Van Buchem disease. Furthermore, sclerostin is almost exclusively expressed in the osteocytes and *sost* knockout mice have an increased bone mass. These findings point to sclerostin as a promising drug target for osteoporosis. Several pharmaceutical companies are developing sclerostin antibodies (Romosozumab, Blosozumab and BPS804) as treatment for osteoporosis. Most advanced are the studies of Romosozumab (Amgen), a humanized monoclonal antibody targeting sclerostin which entered phase III of clinical trials. In a recent phase II study, it was shown that monthly subcutaneous injection of sclerostin results in an increased BMD at several sites in post-menopausal women with low bone mass. Based on bone turnover markers the study demonstrated that Romosozumab effects bone formation rapidly and clear, however, the effect is transient. This is in contrast with the effect on bone resorption which is moderate but continuous during the period of treatment [60].

Besides a function of sclerostin antibodies in the treatment of postmenopausal osteoporosis, the efficacy of these antibodies is also tested in several animal models with monogenic osteoporosis. Both in a model for osteoporosis pseudoglioma (*lrp5^{-/-}* mouse) and in a model for osteogenesis imperfecta (*Brtl^{+/+}* mouse) inhibition of sclerostin can improve bone mass and decrease fractures [61, 62]. The effect of complete deletion of sclerostin in the OPPG mouse was also studied in an *lrp5/sost* double knockout mouse model. These double knockout mice have larger and stronger bones than *lrp5^{-/-}* mice, indicating that sclerostin acts also through LRP5 independent pathways to increase bone mass.

In addition to sclerostin, there are several other modulators of the canonical Wnt signaling pathway. Recently, it was shown that both in patients and mice lacking sclerostin, expression of

dickkopf1 (**DKK1**), another inhibitor of the pathway, is upregulated [63, 64]. Complete deletion of *dkk1* in mice is lethal, but a heterozygous *dkk1*^{+/-} mouse model has an increased bone mass [65]. These data indicated that DKK1 is an interesting target for the treatment of bone disease. Fully human monoclonal DKK1-neutralizing antibodies are currently under study in several animal models for OVX-induced osteoporosis, multiple myeloma and erosive rheumatoid arthritis with promising results. However, more studies are needed. Especially for the management of multiple myeloma, DKK1-antibody treatment (BHQ880, Novartis) looks promising and clinical trials are ongoing (clinicaltrials.gov).

Agent	Current stage	Targeted mechanism	Mechanism of action
RANKL-antibodies (denosumab)	Marketed in 2010	OPG/RANK/RANKL pathway	Binds to RANKL and mimics the effect of OPG preventing RANK activation and subsequent stimulation of osteoclast differentiation, activation and survival.
CLCN7 inhibitors (NS3736)	Preclinical	Osteoclastic bone resorption	Inhibits the acidification of resorption lacunae by blocking chloride ions transport.
Vacuolar ATPase inhibitors (SB242784, FR167356, FR202126)	Preclinical	Osteoclastic bone resorption	Inhibition of resorption lacunae acidification by disruption of main osteoclastic ATP-dependent proton pump.
Cathepsin K inhibitors (Odanacatib, ONO-5334, MIV-711)	Phase III clinical trials	Osteoclastic bone resorption	Inhibition of main cysteine protease of the osteoclast used for bone matrix proteins degradation.
SOST-antibodies (Romosozumab, Blosozumab, BPS804)	Phase III clinical trials	Wnt signaling	Neutralization of Wnt signaling inhibitor that is selectively secreted by osteocytes. Upregulation of the pathway enhances bone formation.
DKK1-antibodies (BHQ880)	Preclinical	Wnt signaling	Neutralization of secreted Wnt signaling inhibitor. Upregulation of the pathway enhances bone formation.

Table 2: Summary of osteoporosis drugs targeting mechanisms highlighted by the research in sclerosing bone dysplasias.

In conclusion, it is clear that the identification of genes responsible for monogenic sclerosing bone disorders not only increase the knowledge on pathways involved in the regulation of bone remodeling but also open new therapeutic avenues for the treatment of patients with osteoporosis.

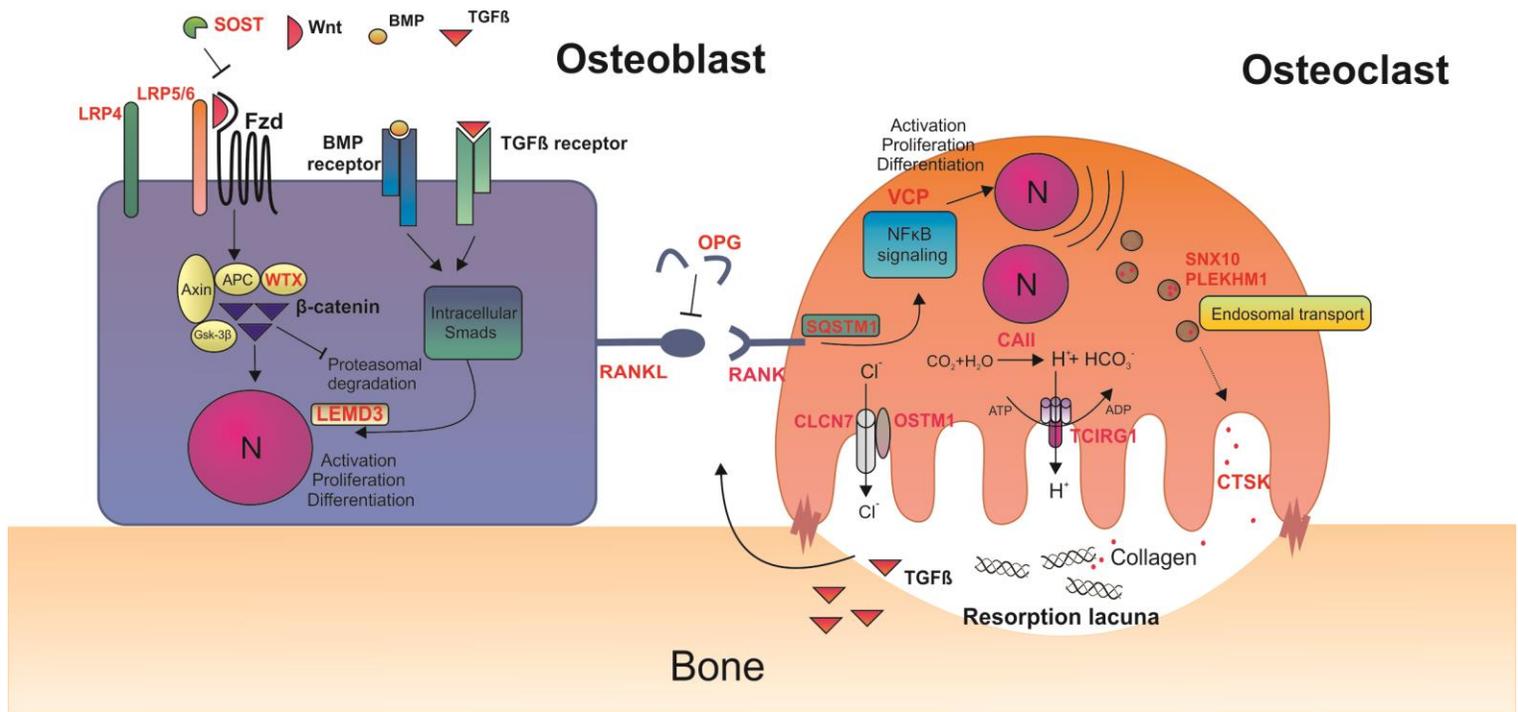


Figure 1: Overview of pathways and mechanisms involved in the pathogenesis of sclerosing bone dysplasias. Gene names were discussed in the text.

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