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# Osteoclast Genetic Diseases

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## 1. Introduction

Bone is a specialized connective tissue that performs many important functions: (i) mechanical, supporting the whole body and allowing the movements; (ii) protective, shielding many vital organs, such as brain, lung, heart and bone marrow; (iii) metabolic, regulating the homeostasis of calcium and phosphate (Baron, 1999); (iv) endocrine, regulating kidney function (Fukumoto & Martin, 2009; Mazzaferro et al., 2010) and contributing to global energy balance (Ducy et al., 1996; Ferron et al., 2010; Lee et al., 2007) and male fertility (Oury et al., 2011). Bone is a dynamic tissue, subjected to a continuous process of renewal and remodelling in which bone resorption by osteoclasts and bone formation by osteoblasts occur at the same site along the bone surface (Pogoda et al., 2005). About 10% of bone is replaced each year, with complete skeletal renewal every 10 years. An imbalance between osteoblast and osteoclast activities can cause serious consequences: if bone formation is enhanced or bone resorption is impaired, bone mass is increased, and *vice versa* (Parfitt, 1982; Pogoda et al., 2005). Often osteoclast diseases are monogenic, and in many of them the responsible gene and the respective function have been identified, while for other osteoclast diseases the causative gene has not been isolated or the exact function of the matching protein still remains unknown. In this review, a brief description of osteoclast biology will be provided and examples of genetic osteoclast diseases, including osteopetrosis, pycnodysostosis and Paget's disease of bone, will be discussed.

## 2. Osteoclast

The osteoclast is the unique cell that is able to destroy the tissue to which it belongs (Teitelbaum, 2007). It is a giant cell with a diameter of 20-100 μm containing 4 to 50 nuclei, depending on the species (Roodman, 1996). The multinuclearity of osteoclast derives from the fusion of monocyte-macrophage mononuclear cells (Figure 1). In histological sections, osteoclasts appear variable in shape and size, adherent to the bone, within a small depression, called Howship's lacuna, that is the result of their bone resorbing activity (Roodman, 1996). Osteoclasts are polarized cells (Takahashi et al., 2007). In fact, it is possible to identify a zone facing the bone matrix presenting a particular area of the plasma membrane, named ruffled border, composed by deep and irregular foldings that increase the size of the membrane located in front of the bone that will be resorbed (Stenbeck, 2002). The peripheral domain, named "sealing membrane", represents the adhesion area by which the osteoclast attaches to the bone matrix around the site where it will be degraded. The

remaining membrane constitutes the basolateral domain containing proteins important for ion balance and response to regulatory stimuli. Opposite to the ruffled border domain, there is the apical domain, that is thought to be important for the transcytosis of bone resorption products from the resorbing lacuna to the extracellular fluids (Coxon & Taylor, 2008; Nesbitt & Horton, 1997; Peruzzi & Teti, 2011; Salo et al., 1996; Takahashi et al., 2007). Underneath the apical domain there are the nuclei that, under the light microscope, appear different in shape: some are round and euchromatic, others are irregular and more heterochromatic (Baron, 1989).

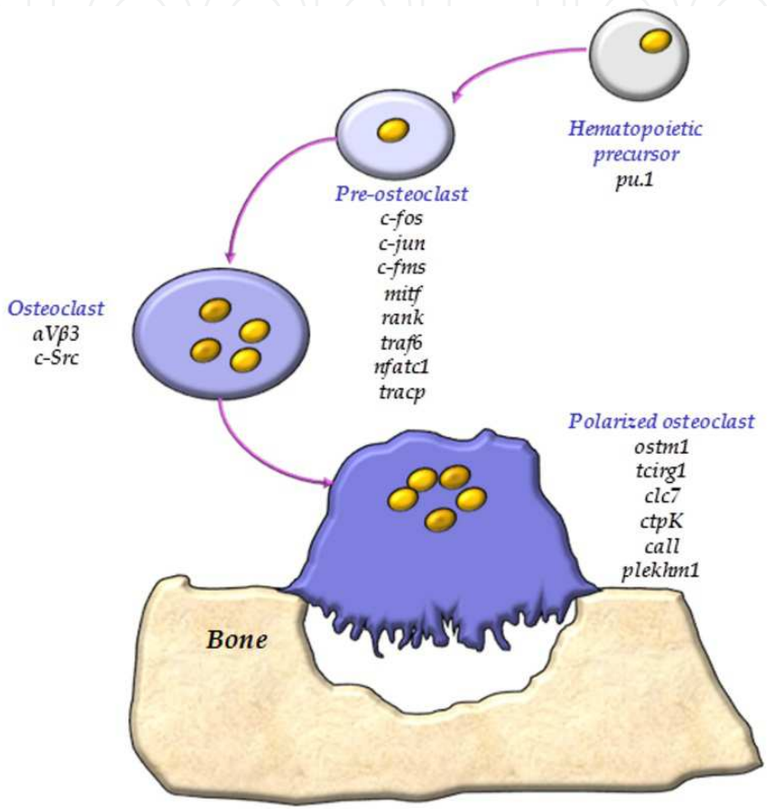


Fig. 1. Osteoclast differentiation. The cartoon illustrates the different phases of osteoclast differentiation, from the hematopoietic precursor to the mature multinuclear osteoclast. Some of the genes implicated in this process are indicated.

Moreover, ultrastructural studies showed Golgi complexes associated with each nucleus, many mitochondria and lysosomes (Baron et al., 1988; Stembeck, 2002). These latter organelles, approximately 0.5 μm in diameter, contain acid hydrolases, such as cathepsin K and Tartrate Resistant Acid Phosphatase (TRAcP), representing markers of the osteoclast phenotype (Garnero, 1998; Sakigiyama et al., 2001). Mitochondria are very abundant, correlating with the high energy expenditure that is required for the degradation of bone matrix (Miyazaki et al., 2006).

### 2.1 The molecular mechanisms of bone resorption

Bone resorption is a complex process requiring two different phases, the acidification of the extracellular lacuna to dissolve the inorganic bone matrix and the secretion of proteolytic

enzymes to digest the organic components (Blair et al., 1986; Vaananen et al., 1998) (Figure 2). To achieve the acidification of the resorption lacunae and begin the process of bone demineralization, Carbonic Anhydrase II (CAII) generates carbonic acid from the hydration of $CO_2$. Carbonic acid spontaneously dissociates in proton and bicarbonate (Bothwick et al., 2003; Boyle et al., 2003). The protons so generated are actively released in the resorbing lacuna through an osteoclast-specific vacuolar-type (V)-$H^+$-ATPase (Nishi & Forgac, 2002; Teitelbaum & Patrick, 2003). The excess of bicarbonate is removed by a bicarbonate/chloride exchanger, localised in the basolateral membrane (Baron, 1989; Teti et al., 1989). The chloride ion is then released in the bone resorption lacuna by a $Cl^-/H^+$ antiport, ClC7, that, coupling with the proton pump activity, balances the ion charge across the membrane (Boyle et al., 2003; Graves et al., 2008; Teitelbaum & Patrick, 2003). The final goal of this process is to demineralise the bone and uncover the organic matrix ready to be digested by proteolytic enzymes, such as the metalloproteinase MMP9 released by endosomal vesicles, and the cathepsin K released by lysosomes (Blair et al., 1986; Bossard et al., 1996; Everts et al., 1992).

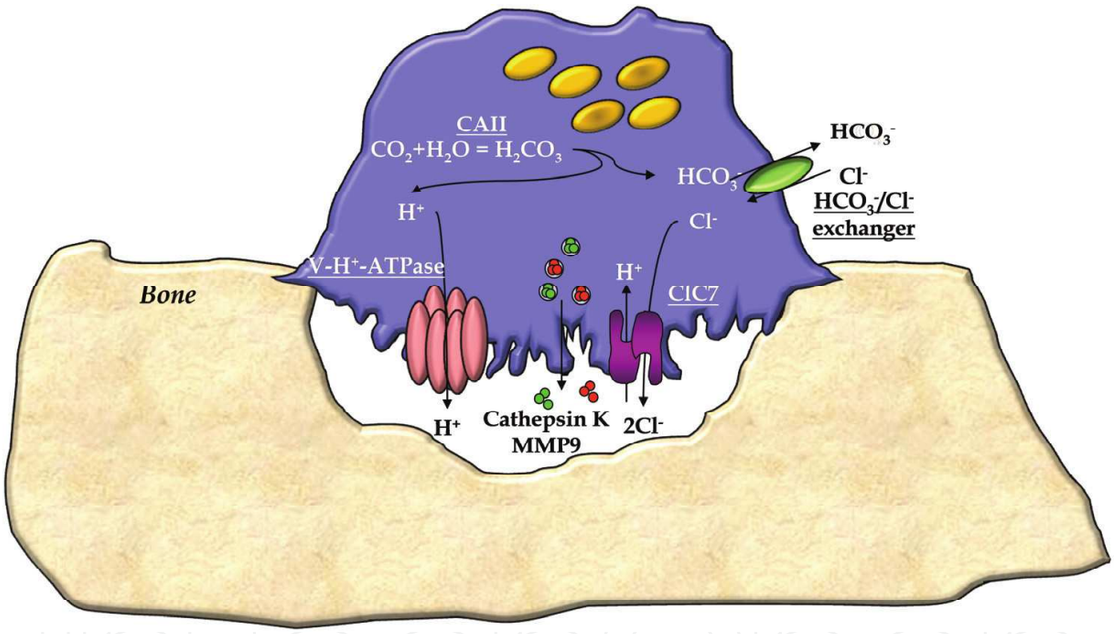


Fig. 2. The bone resorption process. The cartoon illustrates the molecular patterns involved in bone resorption by osteoclasts. See text for detailed description.

### 2.2 Osteoclastogenesis and regulation of osteoclast activity

Osteoclasts are cells that belong to the monocyte/macrophage lineage and derive from the fusion of monocuclear precursors (Teitelbaum, 2007) (Figure 1). In 1981, Marks and Walker showed, by experiments with parabiotic animals, that circulating blood contains cells able to differentiate into osteoclasts, thus identifying their haematogenous origin (Marks & Walker, 1981). Subsequently, in vitro studies with bone marrow-derived cells (Burger et al., 1989) suggested that osteoclasts arise from the differentiation of precursor cells of the CFU-M (Colony Forming Unit-Macrophage) lineage. This evidence suggested that osteoclasts present the same haematopoietic origin of antigen presenting cells and tissue macrophages. The pathway of osteoclast differentiation is now well characterized (Teitelbaum et al., 1997).

The PU.1 transcription factor is essential for the earliest phase of osteoclast differentiation, regulating the expression of the *c-fms* gene (Hayashi et al., 1998). *c-fms* encodes for the receptor of M-CSF (Macrophage-Colony Stimulating Factor), a cytokine crucial for the survival and the proliferation of early progenitors since it stimulates the cyclinD/CDK4 (Cyclin-Dependent Kinase 4) pathway (Mundy, 1993; So et al., 2003). Moreover, c-fms is able to stimulate the expression of PU.1 itself, establishing an amplification loop (Mundy, 1993). The essential role of PU.1 during osteoclast commitment is even due to its ability to regulate the expression of RANK (Receptor Activator of NF-κB) that, upon interaction of its ligand RANKL, is able to initiate the differentiation and the fusion of osteoclast precursors (Kwon et al., 2005). In fact, subsequent to RANKL-RANK interaction, TRAF6 (TNF Receptor-Associated Factor 6) is recruited and activates IκB and MAP kinases (Takayanagi et al., 2005), causing the nuclear translocation of NF-κB and of other transcription factors, including ATF2 (Activating Transcription Factor 2), c-fos and c-jun, required for the progression of osteoclast differentiation (Wada et al., 2006). Other two transcription factors important for osteoclast differentiation are MITF (MIcrophthalmia-associated Transcription Factor) (So et al., 2003) and NFATc1 (Nuclear Factor of Activated T-cells, cytoplasmic, calcineurin-dependent 1) (Takayanagi, 2007) that regulate the expression of osteoclast specific genes, like *TRAcP*, *OSCAR* (OSteoClast-Associated immunoglobulin-like Receptor), *CTSK*, *CLC7* and *OSTM1* (OSteopetrosis associated TransMembrane protein) (Takayanagi, 2007; Meadows et al., 2007). The activation of RANK by RANKL is counterbalanced by the expression of a soluble decoy receptor, OPG (OsteoProteGerin), that is able to bind RANKL, preventing its interaction with RANK (Kong et al., 1999). The expression of RANKL by stromal cells and, during inflammation, by T cells and synovial fibroblasts, is regulated by hormones and local factors as it is stimulated by PTH (ParaThyroid Hormone), $PGE_2$ (ProstaGlandin $E_2$) and $1,25(OH)_2$Vitamin $D_3$ (Lips, 2006; Parfitt, 1976; Takeda et al., 1999). According to other studies, osteoclast progenitors express $1,25(OH)_2$Vitamin $D_3$ receptors and their activation could contribute to the induction of RANK (Blair & Zaidi, 2006). Even sex hormones regulate osteoclast differentiation and function (Manolagas et al., 2002). Estrogens and androgens are believed to attenuate the rate of osteoclast formation downregulating genes essential for osteoclastogenesis (Cheung et al., 2003; Girasole et al., 1992; Imai et al., 2009) and exerting a potent pro-apoptotic effect. Glucocorticoids are also thought to target the osteoclasts, preventing cell spreading and reducing their bone resorbing activity (Dempster et al., 1997; Kim et al., 2007). However, the use of glucocorticoids leads to a reduction of bone mass due to a direct negative effect on osteoblast activity and to inhibition of osteoclasts, that result in the interruption of the bone remodeling cycle (Dovio et al., 2004). Furthermore, osteoclasts are very sensitive to pH levels as it is known that systemic acidosis has detrimental effects on the skeleton and local acidosis is associated with bone destruction (Arnett, 2003; Krieger et al., 2004; Muzylak et al., 2007). It has been shown that the Ovarian cancer G-protein-coupled Receptor 1 (OGR1 or GPR68), a proton sensing receptor, is essential for osteoclast formation inducing RANKL-dependent osteoclastogenesis and activating NFATc1 (Iwai et al., 2007).

## 3. Osteopetrosis

Osteopetrosis is a rare (>1:100.000) genetic disorder characterized by an impaired osteoclast function that leads to pathological increase of bone mass and skeletal fragility. It was identified for the first time in 1904 by Albers-Scönberg, who described a patient

with generalized sclerosis of the skeleton, suffering from several fractures (Albers-Schönberg, 1904). Subsequently, in 1926, Karshner denominated the syndrome "marble bone disease" or "osteopetrosis" (Karshner, 1926). Impaired bone resorption causes persistence of old bone, increase of bone mass and obstruction of cavities containing vital organs such as the bone marrow and the nervous system. Osteopetrotic patients usually suffer from pathological fractures, short stature and haematological and neural failures (Balemans et al.; 2005; Del Fattore et., 2008; Frattini et.; 2003; Loria-Cortes et al., 1977). Osteopetrosis is a heterogeneous disorder which includes several forms that differ on the basis of inheritance, severity and secondary clinical features (Balemans et al., 2005). So far, there is no effective cure for osteopetrosis (Del Fattore et al., 2010). Haematopoietic Stem Cell Transplantation (HSCT) is indicated only for some severe forms; however a large rate of unsuccessful engraftment and persistence of irreversible symptoms are frequently observed (Driesses et al., 2003).

### 3.1 Clinical features and genetic inheritance

The various forms of osteopetrosis are classified on the basis of clinical, radiological and inheritance features into three major groups (Balemans et al., 2005; Whyte, 2002): the Autosomal Recessive Osteopetrosis (ARO), the Intermediate autosomal Recessive Osteopetrosis (IRO) and the Autosomal Dominant Osteopetrosis (ADO). Although these forms display different symptoms, they share common clinical traits such as increase of bone density, spontaneous fractures and haematological failures (Del Fattore et al., 2008). ARO is the most severe form and it is commonly diagnosed soon after birth or within the first years of life. Patients display a generalised osteosclerosis, especially in skull, pelvis, spine and long bones (Frattini et al., 2000; Kornak et al., 2000; Loria-Cortes et al., 1977), which display the so-called "bone in bone" appearance (Figure 3). The poor development and/or compression of the bone marrow and the nervous system leads to severe anaemia, pancytopenia, hepatosplenomegaly, visual impairment, optic atrophy and deafness. Less common features are hydrocephaly, macrocephaly and strabismus. In a subtype of ARO primary degeneration of brain and retina are observed (Askmyr et al., 2008). Unfortunately, a fatal outcome generally occurs in 75% of ARO patients, who die at 3-4 years of age because of haematological failure and recurrent infections (Balemans et al., 2005).

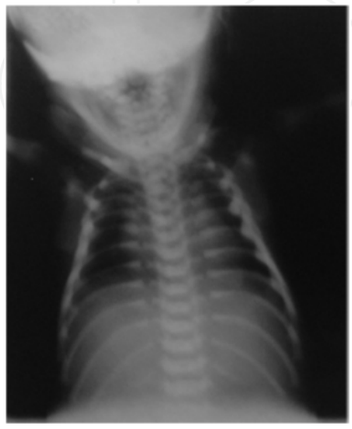

Fig. 3. X-ray analysis illustrating generalized osteosclerosis in an ARO patient. The picture shows the extensive sclerosis of spine, ribs and skull.

IRO is milder than ARO and life expectancy is much longer. Typical symptoms of this form are generalized increase of bone density, osteomyelitis, short stature, dental malformations, and mild to moderate anaemia (Balemans et al., 2005; Bolt et al., 2005; Del Fattore et al., 2010; Sly et al., 1983). The Autosomal Dominant Osteopetrosis, also called Albers-Schönberg disease (Albers-Schönberg, 1904), was previously described inappropriately as the "benign form" but it is now accepted as an extremely heterogeneous osteopetrosis, ranging from asymptomatic to severe (Del Fattore et al., 2006; Frattini et al., 2003; Waguespack et al., 2007). This phenotypic variability is even observed within the same family (Letizia et al., 2004). ADO patients usually present with sclerosis of skull base, pelvis, and vertebral end-plates (Figure 4) (sandwich vertebrae or rugger-jersey spine), bone pain, osteomyelitis and frequent pathological fractures. Life expectancy is generally normal, but in some cases complications due to cranial nerve compression, a rather poor quality of life and death have been reported (Albers-Schönberg, 1904; Balemans et al., 2005; Del Fattore et al., 2006).

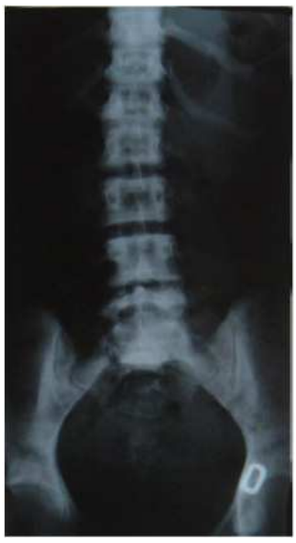

Fig. 4. X-ray analysis of an ADO patient showing sclerosis of vertebral end-plates (sandwich vertebrae) and pelvis.

Besides these classical forms, five male cases have been described so far with X-Linked Osteopetrosis (XLO) associated with lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency (so-called OL-EDA-ID syndrome). They died very young for severe phenotype and infection complications (Smahi et al., 2002).

### 3.2 Genetic features

The extreme phenotypic variability of osteopetrosis arises from the genetic heterogeneity. As shown in Table 1, in osteopetrotic patients mutations in genes encoding proteins essential for correct bone resorption or for osteoclast differentiation have been observed. As discussed above, these mutations can be inherited in an autosomal recessive, autosomal dominant or X-linked manner (Del Fattore et al., 2010). ARO, the most severe form, is due in more than 50% of cases to loss-of-function mutations of the *TCIRG1* gene, encoding for the osteoclast-specific a3 subunit of V-$H^+$-ATPase (Del Fattore et al., 2006; Frattini et al., 2000; Kornak et al., 2000; Taranta el al., 2003).

| Gene | Protein | Type of mutation | Form of osteopetrosis |
|---|---|---|---|
| *TCIRG1* | a3 subunit of vacuolar $H^+$-ATPase | Loss-of-function | ARO |
| *TCIRG1/ATP6V1B1* | a3/B1 subunits of vacuolar $H^+$-ATPase | Loss-of-function | ARO |
| *CLC7* | Chloride/proton antiport | Loss-of-function | ARO |
| | | Dominant negative | ADO |
| *OSTM1* | Trasmembrane protein associated with ClC7 function | Loss-of-function | ARO |
| *PLEKHM1* | Protein with undefined function, probably associated with vesicular trafficking and acidification | Loss-of-function | IRO |
| *CAII* | Carbonic anhydrase type II | Loss-of-function | IRO |
| *NEMO* | Regulatory subunit of IKK | Loss-of-function | XLO |
| *TNFSF11* | Receptor activator of NF-kB ligand (RANKL) | Loss-of-function | ARO |
| *TNFRSF11A* | RANK | Loss-of-function | ARO |

Table 1. Genetic defects in human osteopetroses

The V-$H^+$-ATPase is central to the mechanism of bone resorption because it is located in the osteoclast ruffled border membrane where it releases protons in the underneath resorbing lacuna (Nishi & Forgac, 2002). In rare cases, double mutations of the *TCIRG1* gene and the *ATP6V1B1* genes, this latter encoding the B1 subunit of V-$H^+$-ATPase, were described (Bothwick et al., 2003). As shown in Table 1, other four genes are associated with ARO. About 10-15% of patients harbours mutations of the *CLC7* gene (Frattini et al., 2003; Kasper et al., 2005; Kornak et al., 2001), encoding for the so called chloride channel type 7, recently reclassified as a $Cl^-/H^+$ antiport (Graves et al., 2008). This dimeric protein is located in lysosomes and osteoclast ruffled membrane where, as previously described, it is essential to restore the correct electrical potential altered by proton flux (Graves et al., 2008). So far, only 5 patients affected by ARO were found to harbour loss-of-function mutations of the *OSTM1* gene, encoding for a protein whose role in bone resorption is still unknown (Chalhoub et al., 2003; Pangrazio et al., 2006). Ostm1 function is probably important for $Cl^-$ conductance, because it was recently shown that the protein is involved in the stabilization and correct localization of the $Cl^-/H^+$ antiport (Lange et al., 2006). The correlated functions of ClC7 and Ostm1 proteins are demonstrated by the similar clinical features of patients harbouring mutations of the respective genes (Pangrazio et al., 2006). Primary retinal degeneration and lysosomal storage disease are observed in these patients, who are believed not to benefit from HSCT because it cannot cure the neural defects. Beside the types of AROs described above, so-called "osteoclast-rich" osteopetroses because in these forms osteoclasts form normally or are even increased in number, there is also a particularly rare form of ARO where the osteoclasts are absent (Helfrich, 2005). The patients affected by this "osteoclast-poor" osteopetrosis present mutations of the *TNFSF11* (Sobacchi et al., 2007) or the *TNFRSF11A* (Guerrini et al., 2008) genes (Table 1), encoding the RANKL and its receptor

RANK, respectively. Both proteins are required for osteoclast differentiation. So far, only 6 patients have been described to carry mutations of the *TNFSF11* gene. The importance of this discovery relies on the fact the these patients could not be effectively treated with HSCT, because the genetic defect is not osteoclast-autonomous but rather relies on the inability of stromal/osteoblastic cells to produce RANKL. ADO, the most frequent osteopetrosis, is caused in about 70% of patients by heterozygous dominant negative mutations of the *CLC7* gene (Bollerslev et al., 1988; Del Fattore et al., 2005; Frattini et al., 2003; Letizia et al., 2004; Waguespack et al., 2007). *CLC7* gene mutations tend to affect the entire length of the gene, even if the most frequent mutations have been described in the regions encoding the C-terminal CBS (Cystathionine Beta Synthase) domains of the protein (Del Fattore et al., 2006; Waguespack et al., 2007). As described above, ADO is characterized by a phenotypic variability probably due to the incomplete penetrance of the mutant gene (Frattini et al., 2003; Letizia et al., 2004). No other genes are known so far to be correlated with ADO and about 30% of patients still lacks a genetic diagnosis (Del Fattore et al., 2010). As in ADO, also in IRO a considerable clinical heterogeneity is observed. Presently, the two genes known to be associated with IRO are *CAII* (Bolt et al., 2005) and *PLEKHM1* (Van Wesenbeeck et al., 2007), encoding the carbonic anhydrase type II and the Plekhm1 protein, respectively. Patients harbouring loss of function mutations of the *CAII* gene display, besides osteopetrosis, tubular acidosis, cerebral calcifications and mental retardation (Balemans et al., 2005). The novel gene recently associated with osteopetrosis, *PLEKHM1*, has been identified as the human homolog of the gene responsible of the *incisor absent* (ia) rat phenotype (Van Wesenbeeck et al., 2007). To date, only one female patient affected by IRO has been identified to harbour a mutation of the *PLEKHM1* gene. The clinical features described in this patient were increased bone density, Erlenmeyer flask' deformity of the distal femora and a chondrolysis of the left hip. The exact function of the Plekhm1 protein is not completely elucidated, but recent findings suggest that it is a member of Rab7-regulated proteins involved in late endosomal trafficking (Del Fattore et., 2008; Van Wesenbeeck et al., 2007), vesicular acidification and TRAcP release by osteoclasts (Del Fattore et al., 2008). As previously described, there is a XLO osteopetrosis, due to mutations of the *NEMO* (NF-κB Essential Modulator) gene, encoding the IκB regulatory subunit of IKK. The mutations described in the only 5 so far known patients cause the replacement of the *NEMO* stop codon with tryptophan, leading to the addition of 27 irrelevant residues that strongly destabilize the protein (Smahi et al., 2002). All other forms of osteopetrosis, about 30% of patients, still lack of a recognized gene involved and much effort should be made to identify new genes associated with this disease.

## 4. Pycnodysostosis

Pycnodysostosis is a skeletal disorder also known as Toulouse-Lautrec disease because it is believed that the famous French painter Henri Toulouse-Lautrec (1864-1901) suffered from this syndrome (Maroteaux & Lamy, 1965). It is a rare monogenic disease (approximately 150 cases reported in the literature worldwide), first described in 1962 by Maroteaux and Lamy, who coined this term from the word of Greek origin *puknos* meaning "dense", associated with the words *dys* meaning "defective" and *ostosis* meaning "condition of the bone". Pycnodysostosis is characterised by a general osteosclerosis leading to short stature and increased bone mass. In fact, Schilling and coworkers analysed the volumetric bone density

in a cohort of pycnodysostosis patients and controls showing a value of 686 mg/cm in the group of patients versus 290 mg/cm in the control group (Shilling et al., 2007). This disease appears to be especially common among the Japanese, but many cases are even described in Europe and United States (Muto et al., 1991).

### 4.1 Clinical features

The diagnosis of pycnodysostosis is usually performed during infancy or early childhood because of increased bone mass, short stature and cranial dysplasia. Pycnodysostosis could be confused with osteopetrosis, although it has peculiar features such as gracile clavicles with hypoplastic ends, obtuse mandibular angle, enlarged skull with opened anterior fontanel and cranial sutures, and acroosteolysis of distal phalanges (Soliman et al., 2001). Moreover, in pycnodysostosis anaemia and hepatosplenomegaly have not been reported. The exfoliation of deciduous teeth is usually altered, as well as the eruption of the permanent dentition. Endobones and radiodense striations are absent. As in osteopetrosis, pycnodysostosis patients may suffer from frequent fractures since the first year of life. Moreover, fractures of the mandible during tooth extractions have been described. Lower limbs seem to be particularly involved in fractures, resulting in *genu valgu* deformity. About 10% of the patients show mental retardation. Moreover, recurrent respiratory infections and right heart failure have been described (Muto et al., 2005).

### 4.2 Genetic inheritance

Pycnodysostosis is an autosomal recessive disease caused by mutations of the *CTSK* gene. In 1995, Gelb and coworkers first mapped the disease in a narrow region on chromosome 1q21 with a maximal lod score of 11.72 (Gelb et al., 1996). In 1996, they identified the mutated gene, *CTSK*, encoding the cathepsin K, a cystein proteinase expressed in many tissues such as bone, ovary, colon, skeletal muscle, placenta and small intestine (Zhao et al., 2009). Cathepsin K is synthesized as an inactive precursor of 329 amino acids (aa). The N-terminal pro-peptide of 99 aa is cleaved between Arg 114 and Ala 115 to supply the mature cathepsin K of 215 aa (Bromme & Okamoto, 1995). In the bone, it plays an important role in bone resorption since it cleaves, at acidic pH, collagen type I, osteopontin and other proteins of the bone matrix (McQueney et al., 1997). Particularly, cathepsin K cuts triple-helical collagen into small peptides. Cleavage occurs in its non collagenous termini (N- and C-telopeptide regions). These fragments can be detected in urine and serum as markers of bone resorption (Atley et al., 2000). Cathepsin K-deficient mice generated by inactivation of the *ctsk* gene display an increase of bone mass as well as radiological and histological abnormalities typical of pycnodysostosis (Gowen et al., 1999; Saftig et al., 1998). The analysis of the genomic DNA indicated that the *CTSK* gene is composed by eight exons and seven introns (Rood et al., 1997). Presently, 27 different types of mutations, spread throughout the whole gene, have been described in 34 unrelated families (Helfrich, 2003; Toral-López et al., 2011). According to bio-informatic analyses, all mutations seem to affect the protein folding, destabilizing the whole structure or creating locally structural changes that could affect the conformation of a small part of the protein (Donnarumma et al., 2007).

## 5. Paget's disease of bone

Paget's disease of bone is a common disorder characterized by increased bone turnover within focal lesions throughout the skeleton. It was described for the first time in 1876 by Sir

James Paget as a disease that "begins in middle age or later . . . affects most frequently the long bones of the lower extremities and the skull". Moreover, he stated that "the bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen" (Paget, 1876). Paget's disease of bone affects both men and woman, with a slight predominance in males (van Staa et al., 2002). Although many patients are often asymptomatic, others have a poor quality of life, with bone pain, skeletal deformities and fractures (Selby et al., 2002). The estimated prevalence of Paget's disease of bone in the world is about 1%, arising up to about 3% in North America, Great Britain, Australia and Western Europe. Conversely, this disease is very rare in Scandinavia and in the Indian subcontinent (Detheridge et al., 1982). These marked geographical differences in the prevalence strengthen the importance of genetic factors involved in the pathogenesis of Paget's disease of bone, but some evidence suggests an important role also for environmental determinants.

### 5.1 Clinical features

Paget's disease of bone is a disorder of bone remodelling. It is very important to underline the localized nature of the disease. It could affect a single bone or only a portion of it, or it could involve more bones (Ralston, 2008). As described above, many patients affected by Paget's disease of bone are often asymptomatic and the diagnosis is usually performed incidentally on the basis of elevated serum alkaline phosphatase levels not correlated with other diseases, or of abnormal skeletal radiographs (Tiegs et al., 2000). Conversely, other patients suffer from mild to moderate bone ache that characteristically begins late in the clinical course (Ralston et al., 2008). The direct cause of pain could be difficult to explain, requiring a careful analysis. An increase of vascularity and consequent warmth usually occur in pagetic bones, leading to unpleasant sensation perceived by patients (Altman, 1980). Micro-fractures that frequently affect the diseased bone can contribute to discomfort. Another typical sign of the disease is skeletal deformity, usually of the femur or tibia, that could aid in the cause of pain onset (Ralston et al., 2008). Moreover, severe secondary osteoarthritis can be observed at joints close to pagetic bones. Patients affected by Paget's disease of bone suffer from fractures that could be either traumatic or pathologic, particularly involving the long bones. The involvement of the skull in the disease complaints occurs in up to one third of the patients, and is characterized by macrocephaly, frontal bossing and hearing loss. Palsies of cranial nerves II, VI and VII could also be observed. Neoplastic degeneration, particularly osteogenic sarcoma involving the pelvis (although both fibrosarcoma and chondrosarcoma are also observed), develop in less that 1% of patients (Reddy et al., 2001).

### 5.2 Genetic inheritance

As aforementioned, both genetic and environmental factors can contribute to the pathogenesis of Paget's disease of bone. In less than 15-40% of cases, this disease is inherited in an autosomal dominant manner, even if many patients do not have a family history (Haslam et al., 1998; Hocking et al., 2000). Seven different loci have been identified by locus linkage studies associated with the onset of the disease. They are located on chromosomes 2p36, 5q31, 5q35, 10p13, 18q21 and 18q23 (Good et al., 2002; Haslam et al., 1998; Hocking et al., 2001; Laurin et al., 2001; Tilyard et al., 1982). Other studies confute this linkage association, showing that the analysis may have false positives (Ralston, 2008).

Subsequently, Laurin et al. and Hocking et al. identified, by positional cloning studies on chromosome 5q35, the *SQSTM1* gene as the most important cause of the disease (Hocking et al., 2002; Laurin et al., 2002). The *SQSTM1* gene encodes the p62/sequestosome 1, an ubiquitously expressed adapter protein involved in several cellular activities, including regulation of NF-κB signalling, autophagy, sequestration of ubiquitinated proteins and inhibition of ERK-MAPK signalling (Mosca & Diaz-Meco, 2002) (Figure 5). Particularly, it was shown that p62 is able to bind TRAF6 and K48- and K63-linked ubiquitin chains via the UBA (UBiquitin-Associated) domain (Figure 5) (Seibenhener et al., 2004). It was shown that sequestosome 1 colocalizes with ubiquitinated protein aggregates, and it has been detected in protein aggregates typical of Alzheimer's and Parkinson's diseases (Paine et al., 2005). Moreover, most of the mutations found in Paget's disease of bone are located in the UBA domains, preventing protein aggregation or, conversely, inducing the formation of aggregates larger than normal (Cavey et al., 2005; Cavey et al., 2006; Yip et al., 2006). However, it is not yet clear what role these aggregates might play in the pathogenesis of Paget's disease of bone.

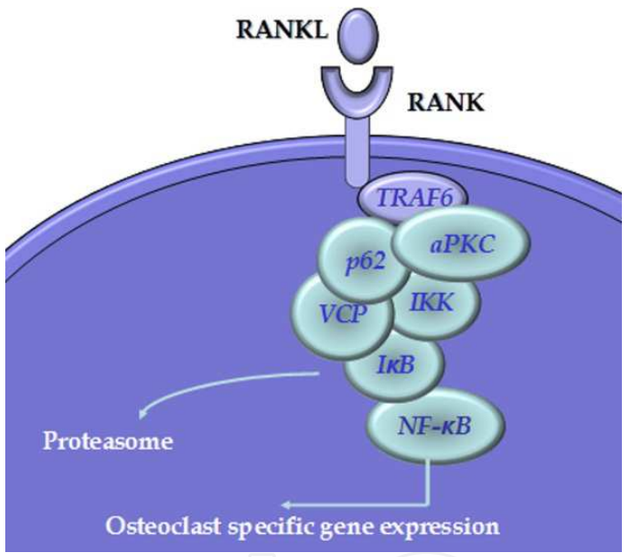


Fig. 5. Sequestosome/p62 pathway in osteoclasts. The binding of RANKL to the receptor RANK results in recruitment of TRAF6, p62 and aPKC (atypical Protein Kinase C). Moreover, the RANKL-RANK interaction leads to the phosphorylation of IKK (Inhibitor of κb kinase), that subsequently phosphorylates IκB (Inhibitor of κB). The phosphorylated IκB is degraded by the proteasome. NF-κB can translocate to the nucleus, inducing the expression of osteoclast specific genes. VCP (Valosin-Containing Protein) is involved in the regulation of IκB degradation by the proteasome.

The first mutation identified in French pagetic patients was the Proline-Leucine mutation affecting codon 392 (P392L) in the UBA domain (Laurin et al., 2002). A transgenic mouse carrying the P392L mutation under the control of the *tracp* promoter was generated and displayed an osteopenic phenotype, with increased number of osteoclasts, but no osteolytic lesions (Kurihara et al., 2000). Another animal model was generated by the group of Ralston, carrying a truncating mutation at serine 409, that developed focal lesions, representing the first true model of the disease (Rojas et al., 2007). Several other genes have been associated

with Paget's disease of bone, such as *TNFSF11, TNFRSF11A* and *TNFRSF11B*, this latter particularly in juvenile disease. However, these association studies still lack a sample size large enough to enable to draw definitive conclusions on the involvement of these genes in the disease (Ralston, 2008).

## 6. Conclusions

Osteopetrosis, pycnodysostosis and Paget's disease of bone are examples of genetic diseases that underlie the essential role of osteoclasts in the regulation of bone homeostasis. They have been instrumental for the understanding of the mechanisms by which osteoclasts form and resorb bone and contributed to shed light on the pathogenesis of more frequent bone diseases, including osteoporosis and bone inflammatory disorders, such as osteoarthritis and rheumatoid arthritis (Tanaka et al., 2005). Further investigation on osteoclast genetic diseases is expected to help increase our knowledge about the recently identified relationships between the bone and other systems, including the immune system (Takayanagi, 2010), the nervous system (Kumar et al., 2010), the endocrine system (Ferron et al., 2010; Fukumoto & Martin, 2009; Karsenty & Oury, 2010), the reproductive system (Oury et., 2011) and the skeletal muscle system (Rufo et al., 2011), in which osteoclasts may be implicated. Therefore, in the next future we are likely to assist to flourishing novel insights into the osteoclast biology, physiology and pathology, which could represent the basis for a better prophylaxis and more effective treatments of bone diseases.

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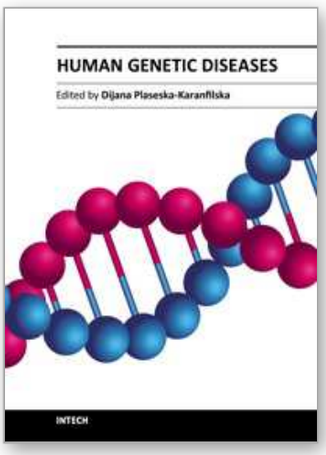


**Human Genetic Diseases**

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The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the â€œgenetic approachâ€ to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.



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