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REVIEW ARTICLE

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The Role of Molecular Triad OPG/RANKL/RANK Axis in Osteoporosis- A Mini-Review

Wasil Hasan, *Abbas Ali Mahdi and Najmul Islam

Department of Biochemistry, Faculty of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, India

***Department of Biochemistry, King George Medical University, Lucknow, U. P., India**

ABSTRACT

The discovery of the molecular triad receptor activator of nuclear factor-kappa B (RANK)/ RANK ligand (RANKL)/osteoprotegerin (OPG) axis in the mid 1990s for the regulation of bone resorption has led to major advances in our understanding of how bone modeling and remodeling are regulated [Patil and Desai, 2014; Boyce and Xing, 2008]. This system has helped in elucidating a key signaling pathway between stromal cells and osteoclasts [Wittrant et al., 2004].This system is the dominant and final mediator of osteoclastogenesis. OPG, RANKL and RANK are the members of the tumor necrosis factor super family of ligands and receptors. These three factors play a decisive role in regulating bone metabolism. This was demonstrated by the findings of extremes of skeletal phenotypes (osteoporosis vs. osteopetrosis) in mice with altered expression of these molecules [Khosla, 2001]. These tumor necrosis factor super family members also have important functions outside bone [Boyce and Xing, 2007].

Keywords:

INTRODUCTION

Bone homeostasis involves the constant remodeling and rebuilding of bone. While the bone formation side of the equation is carried out by the mesenchymal lineage-derived osteoblasts, the remodeling side of the homeostasis equation in bone is carried out by the hematopoietic lineage osteoclast [Marcus *et al.*, 2008].

Excessive resorption by osteoclasts may lead to pathological destruction such as osteoporosis. Osteoclasts are bone-specific multinucleated cells generated from hematopoietic monocyte precursor cells through differentiation processes primarily governed by two key cytokines receptor activator of nuclear factor kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) [Moon *et al.*, 2012].

Osteoprotegerin (OPG)

It is also known as osteoclastogenesis inhibitory factor (OCIF) or tumor necrosis factor receptor super family member 11B (TNFRSF11B). It is a protein that in humans is encoded by the TNFRSF11B gene [Wada *et al.*, 2006]. The initial cloning and characterization of OPG as a soluble, decoy receptor for RANKL belonging to the TNF receptor super family was the first step that eventually led to an unraveling of this system [Simonet *et al.*, 1997; Khosla, 2001]. OPG is a basic glycoprotein comprising 401 amino acid residues arranged into 7 structural domains. It is found as either a 60-kDa monomer or 120-kDa dimer linked by disulfide bonds [Schoppet *et al.*, 2002]. RANKL activity can be blocked by the soluble decoy receptor OPG, resulting in prevention of bone resorption [Simonet *et al.*, 1997]. Thus, OPG is the naturally occurring inhibitor of osteoclast differentiation [Patil and Desai, 2014]. OPG is produced by a lot of cell types, such as bone-marrow stromal cells and osteoblasts. OPG protects bone from excessive resorption by binding to RANKL with high affinity and preventing or blocking it from binding to RANK [Patil and Desai, 2014; Boyce and Xing, 2008]. It blocks the fusion/differentiation stage of osteoclast precursors, rather than the proliferation stage, by binding to RANKL. Thus, the relative concentration of RANKL and OPG in bone is a major determinant of bone mass and strength [Boyce and Xing, 2008].

Receptor activator of NF-κB ligand (RANKL)

RANKL is the molecule which is blocked by OPG. It is also known as tumor necrosis factor ligand super family member 11 (TNFSF11), TNF-related activation-induced cytokine (TRANCE), osteoprotegerin ligand (OPGL) and osteoclast differentiation factor (ODF) is a protein that in humans is encoded by the TNFSF11 gene [Wong *et al.*, 1997; Anderson *et al.*, 1997; Yasuda *et al.*, 1998; Lacey *et al.*, 1998]. RANKL is one of the critical mediators of osteoclastogenesis [Bharti *et al.*, 2004]. RANKL is the most important locally produced pro-osteoclastogenic factor/cytokine that, in combination with M-CSF, induces osteoclast formation in vitro [Wittrant *et al.*, 2004]. RANKL is expressed as a membrane-bound protein on the surface of osteoblasts, osteocytes and marrow stromal cells [Lacey *et al.*, 1998]. In addition, activated T cells secrete RANKL as a soluble molecule [Kong *et al.*, 1999]. Most osteotropic factors such as IL-1, IL-11, PGE2 and 1,25-$(OH)_2D_3$ induce osteoclast formation by binding to marrow stromal cells, which in turn express increased levels of soluble or membrane forms of RANKL [Wittrant *et al.*, 2004]. It was identified as the key mediator of osteoclastogenesis in both a membrane- bound form expressed on preosteoblastic/stromal cells and T cells as well as a soluble form [Suda *et al.*, 1999; Wong *et al.*, 1999; Khosla, 2001; Theill *et al.*, 2002]. Under physiologic conditions, osteoblasts produce CSF-1 and the differentiation-inducing factor, RANKL [Yoshida *et al.*, 1990; Amano *et al.*, 1998; Lacey *et al.*, 1998; Yasuda *et al.*, 1998]. Osteoclastic activity is triggered via the osteoblasts' surface-bound RANKL

activating the osteoclasts' surface-bound RANK. The RANKL/RANK interaction is needed for differentiation and maturation of osteoclast precursor cells to activate osteoclasts and for the survival of mature osteoclasts [Patil and Desai, 2014]. The binding of RANKL to the RANK receptor activates NF-κB signaling leading to the formation of mature multinucleated osteoclasts [Wada *et al.*, 2006]. The activity of RANKL is balanced by the level of expression of its inhibitor osteoprotegerin OPG. It is the local ratio of RANKL to OPG that ultimately determines if osteoclast formation will occur by regulating the amount of available RANKL. Therefore, RANKL/OPG ratio is an important determinant of bone mass and skeletal integrity [Boyce and Xing, 2007]. RANKL induces osteoclastogenesis through the activation of NF-κB [Bharti *et al.*, 2004].

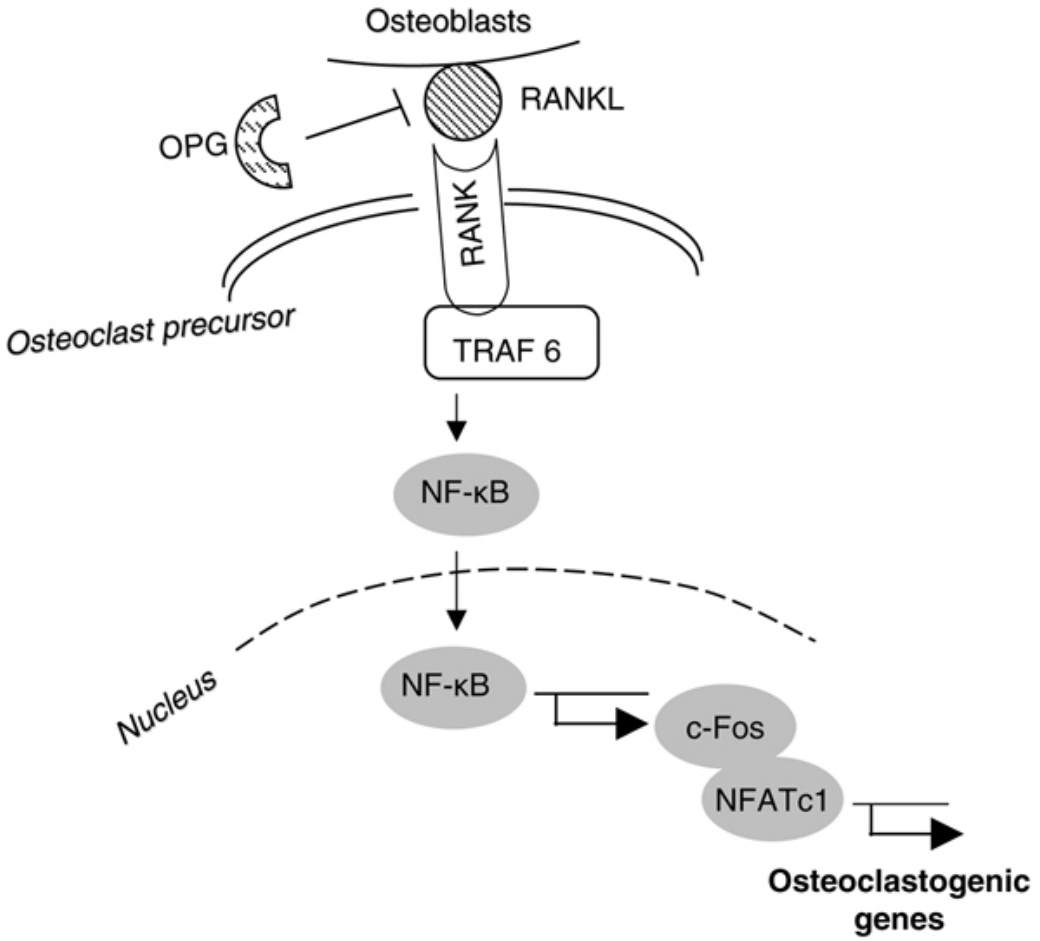

Figure 1. The Signaling Pathway for normal osteoclastogenesis [Boyce and Xing, 2007].

OPG can reduce the production of osteoclasts by inhibiting the differentiation of osteoclast precursors into osteoclasts and also regulates the resorption of osteoclasts *in vitro* and *in vivo*. Thus, in this way, OPG protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from binding to its receptor, RANK [Raisz, 2005; Boyce and Xing, 2007]. By binding RANKL, OPG inhibits NF-κB which is a central and rapid acting

transcription factor for immune-related genes, and a key regulator of inflammation, innate immunity, and cell survival and differentiation [Krakauer, 2008]. OPG levels are influenced by voltage-dependent calcium channels Cav 1.2. OPG also protects arteries from medial calcification [Boyce and Xing, 2007]. Space shuttle flight STS-108 in 2001 tested the effects of OPG on mice in microgravity, finding that it did prevent increase in resorption and maintained mineralization [Bateman and Countryman, 2002]. OPG production is stimulated in vivo by the female sex hormone estrogen as well as the osteoporosis drug, strontium ranelate [Khosla, 2001].

Receptor Activator of Nuclear Factor κ B (RANK)

RANK is stimulated by RANKL. RANK is also called osteoclast differentiation factor receptor (ODFR), TNF receptor super family member 11A (TNFRSF11A) and TNF-related activation induced cytokine receptor (TRANCE-R) [Wada *et al.*, 2006]. RANK is also expressed on dendritic cells and facilitates immune signaling. RANKL then binds to its receptor RANK, present at the surface of osteoclast precursors and mature osteoclasts, inducing osteoclast formation and activation [Nakagawa *et al.*, 1998; Khosla, 2001]. The interaction between RANK and RANKL plays a critical role in promoting osteoclast differentiation and activation leading to bone resorption. The binding of RANKL to its receptor RANK leads to recruitment of the adaptor protein TNF receptor-associated factor 6 (TRAF6) to the cytoplasmic domain of RANK, thereby resulting in the activation of distinct signaling cascades mediated by MAPK, including JNK, p38 MAP kinase (p38), and extracellular signal-regulated kinase (ERK), leading NF-κB activation [Boyle *et al.*, 2003]. NF-κB increases c-Fos expression and c-Fos interacts with NFATc1 to trigger the transcription of osteoclastogenic genes leading to the osteoclast differentiation [Jilka, 2003; Raisz, 2005; Boyce and Xing, 2007]. JNK1- activated c-Jun signaling in cooperation with NFAT is a key to RANKL-regulated osteoclast differentiation [Ikeda *et al.*, 2004]. Stimulation of p38 results in the downstream activation of the microphthalmia/microphthalmia transcription factor (mi/Mitf). This factor controls the expression of the genes encoding TRAP and CTSK, indicating the importance of p38 signaling cascades [Boyle *et al.*, 2003]. RANKL-induced NFATc1 is a downstream event of NF-κB signal pathway [Moon *et al.*, 2012]. RANKL/RANK signaling regulates osteoclast formation, activation and survival in normal bone modeling and remodeling and in a variety of pathologic conditions characterized by increased bone turnover. RANKL/RANK signaling is also required for lymph node formation and mammary gland lactation hyperplasia [Boyce and Xing, 2007]. RANK has been shown to interact with TRAF6 [Junko *et al.*, 2002; Darnay *et al.*, 1998; Darnay *et al.*, 1999; Galibert *et al.*, 1998; Kim *et al.*, 1999], TRAF5 [Darnay *et al.*, 1998; Darnay *et al.*, 1999; Galibert *et al.*, 1998], TRAF1 [Galibert *et al.*, 1998; Kim *et al.*, 1999], TRAF 2 [Darnay *et al.*, 1998; Darnay *et al.*, 1999; Galibert *et al.*, 1998; Kim *et al.*, 1999] and TRAF3 [Galibert *et al.*, 1998; Kim *et al.*, 1999].

CONCLUSION

Thus, as illustrated above, the molecular triad OPG/RANKL/RANK axis plays a very dynamic role in the bone metabolism.

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Corresponding author: Prof. Najmul Islam, Department of Biochemistry, Faculty of Medicine, J. N. Medical College, Aligarh Muslim University, Aligarh 202002, U. P., India
Email: nxi7@hotmail.com