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Review

Regulatory roles and molecular signaling of TNF family members in osteoclasts

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Abstract

The tumor necrosis factor (TNF) family has been one of the most intensively studied families of proteins in the past two decades. The TNF family constitutes 19 members that mediate diverse biological functions in a variety of cellular systems. The TNF family members regulate cellular functions through binding to membrane-bound receptors belonging to the TNF receptor (TNFR) family. Members of the TNFR family lack intrinsic kinase activity and thus they initiate signaling by interacting intracellular signaling molecules such as TNFR associated factor (TRAF), TNFR associated death domain (TRADD) and Fas-associated death domain (FADD). In bone metabolism, it has been shown that numerous TNF family members including receptor activator of nuclear factor κB ligand (RANKL), TNF-α, Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL) play pivotal roles in the differentiation, function, survival and/or apoptosis of osteoclasts, the principal bone-resorbing cells. These TNF family members not only regulate physiological bone remodeling but they are also implicated in the pathogenesis of various bone diseases such as osteoporosis and bone loss in inflammatory conditions. This review will focus on our current understanding of the regulatory roles and molecular signaling of these TNF family members in osteoclasts.

Keywords: Osteoclast; RANKL; TNF-α; FasL; TRAIL; Bone remodeling

Abbreviations: AP-1, activator protein-1; ASK1, apoptosis signal-regulated kinase-1; CARD, caspase recruiting domain; CFU-GM, colony forming unit-granulocyte/macrophage; CRD, cysteine-rich repeat; CTR, calcitonin receptor; DD, death domain; DED, death effector domain; ERK, extracellular signal-regulated kinase; FasL, Fas ligand; FADD, Fas associated death domain; GCKR, germinal center kinase related; HSC, hematopoietic stem cell; IAP, inhibitor of apoptosis protein; IκB, inhibitor of kappa B; IKK, IκB kinase; IL, interleukin; JNK, Jun N-terminal kinase; LT-α, lymphotoxin α; MAPK, mitogen-activated protein kinase; MAP3K, MAPK kinase kinase; MADD, MAP kinase-activating death domain; M-CSF, monocyte/macrophage-colony stimulating factor; MEKK, MAPK/ERK kinase kinase; MKK3, MAPK kinase 3; NF-κB, nuclear factor kappa B; NFAT, nuclear factor of activated T cell; NIK, NF-κB-inducing kinase; OPG, osteoprotegrin; OPGL, osteoprotegrin ligand; ODF, osteoclast differentiation factor; PI3-kinase, phosphoinositide-3OH kinase; PIP3, phosphatidylinositol-(3,4,5)-phosphate; PH, pleckstrin homology; PKB, protein kinase B; RA, rheumatoid arthritis; RANK, receptor activator of NF-κB; RANKL, RANK ligand; RIP, receptor interacting protein; TAK1, TGF-β-activated kinase 1; TGF-β, transforming growth factor β; THD, TNF homology domain; TNF, tumor necrosis factor; TNFR, TNF receptor; TRAF, TNFR associated factor; TRADD, TNFR associated death domain; TRAIL, TNF-related apoptosis-inducing ligand; TRAIL-R, TRAIL receptor; TRAP, tartrate-resistant acid phosphatase; TRANCE, TNF-related activation-induced cytokine; TLR, Toll-like receptor.

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1. Introduction

Since the molecular cloning of cDNAs for TNF-α and lymphotoxin α (LT-α, also named TNF-β), the first two members of the TNF family, in early 1980s (Gray et al., 1984; Pennica et al., 1984), the TNF family has been expanded to include 19 members (Bodmer et al., 2002; Locksley et al., 2001). The TNF family proteins are expressed as type II homo- or hetero-trimeric transmembrane proteins with exception of only one member VEGI, which lacks a predicted transmembrane domain and is therefore synthesized as a secreted soluble protein (Bodmer et al., 2002). Some of the membrane-bound TNF family members may be cleaved at membrane proximal residues to generate soluble forms. Structurally, these proteins are characterized by a conserved domain termed TNF homology domain (THD) in their C-terminal domains, which are the extracellular domains of the membrane-bound members (Pennica et al., 1984). Functionally, despite that the founding members TNF-α and LT-α were initially identified as proteins that possess tumor cytotoxicity, it has been now recognized that members of the TNF family regulate a variety of cellular functions such as cell differentiation, function, survival and/or apoptosis (Gaur and Aggarwal, 2003).

The TNF family members exert the diverse cellular functions by binding and activating their respective receptors belonging to the TNFR family (Bodmer et al., 2002; Locksley et al., 2001). This receptor family consists of 29 known members that are typically single-spanning type I transmembrane proteins with extracellular domains containing two to four homologous cysteine-rich repeats (CRD). However, a few TNFR members exist as secreted soluble proteins. For those members occurring as transmembrane proteins, they have a cytoplasmic domain of variable length bearing little sequence homology (Arch and Thompson, 1999; Bodmer et al., 2002; Darnay and Aggarwal, 1999). Moreover, these TNFR family members can be divided into two subfamilies based on the presence of a death domain (DD) in their cytoplasmic domains: (1) the DD-containing receptors such as TNFR1, Fas, TRAIL-R1 and TRAIL-R2; and (2) the receptors lacking a DD such as RANK, TNFR2, CD27 and CD40 (Arch and Thompson, 1999; Bodmer et al., 2002).

Members of the TNFR family lack intrinsic enzymatic activity in their intracellular domains. As a result, they transduce signaling by recruiting adapter proteins, primarily DD-containing proteins and members of the TRAF family. The DD-containing proteins include FADD and TRADD. These proteins link the DD-containing receptors to downstream proteases of the caspase family necessary for activation of apoptosis. The TRAF family contains six members (TRAFs 1, 2, 3, 4, 5 and 6), each containing a ring and zinc finger motif in their N-terminal and C-terminal domains that mediate self association and protein interaction (Inoue et al., 2000). The TRAFs link either the DD-containing receptors (via other adapter proteins) or the receptor lacking a DD to activation of various signaling pathways such as NF-κB, JNK, ERK and p38 (Baud and Karin, 2001; Locksley et al., 2001).

The TNF family regulates cellular differentiation, function, survival and/or apoptosis in a variety of cell types/tissues/organs. As such, the TNF family has been shown to play important roles in regulating the following key biological processes such as lymphoid organogenesis, acute immune response, inflammation, bone homeostasis, mammary gland development, hair follicle and sweat gland development, and neural development (Locksley et al., 2001). Given the diverse roles the TNF family plays, it could not be possible to discuss the actions of all the TNF family members with enough details in a single review. This review will focus on the regulatory roles of several TNF family members in osteoclast biology and the signaling pathways activated by their corresponding receptors to exert their effects on osteoclasts.

2. The TNF family and osteoclast biology

Osteoclasts are our body's principal bone-resorbing cells that not only play a critical role in skeleton development and maintenance but are also implicated in the pathogenesis of various bone diseases including menopausal osteoporosis (Manolagas, 1998; Pacifici, 2001; Ross and Teitelbaum, 2001). Osteoclasts are multinucleated giant cells that differentiate from cells of hematopoietic origin (Ross and Teitelbaum, 2001; Suda et al., 1992; Teitelbaum et al., 1997). The osteoclast differentiation involves several major stages outlined in Fig. 1. The hematopoietic stem cells (HSC) give rise to circulating mononuclear cells termed colony forming unit-granulocyte/macrophage (CFU-GM). Macrophage/monocyte-colony forming factor (M-CSF) stimulates the proliferation of CFU-GM to maintain a pool of mononuclear cells in monocyte/macrophage lineage, which are widely viewed as osteoclast precursors and characterized by lack of two osteoclast markers: tartrate-resistant acid phosphatase (TRAP) and calcitonin receptor (CTR). The mononuclear precursors are attracted to prospective resorption sites by an unknown mechanism (presumably by chemotaxis) and they will then attach onto bone matrix to differentiate into prefusion osteoclasts with the stimulation of M-CSF and RANKL. The prefusion cells become both TRAP- and CTR-positive. With continuous stimulation of M-CSF and RANKL, the prefusion osteoclasts will further differentiate by fusion to become multinucleated cells. The multinucleated osteoclasts are not functional since they lack the ruffled membrane that is critical for bone resorption. RANKL continue to play an important role in activating osteoclasts by stimulating formation of the ruffled membrane (Jilka et al., 1999; Lacey et al., 1998; Suda et al., 1999). In addition, RANKL also promotes the survival of mature osteoclasts (Fuller et al., 1998; Lum et al., 1999; Wong et al., 1999a).