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Review

RANK Signaling Pathways and Key Molecules Inducing Osteoclast Differentiation

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Mononuclear osteoclast precursors derived from hematopoietic progenitors fuse together and then become multinucleated mature osteoclasts by macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL). Especially, the binding of RANKL to its receptor RANK provides key signals for osteoclast differentiation and bone-resorbing function. RANK transduces intracellular signals by recruiting adaptor molecules such as TNFR-associated factors (TRAFs), which then activate mitogen activated protein kinases (MAPKs), Src/PI3K/Akt pathway, nuclear factor-κB (NF-κB) and finally amplify NFATc1 activation for the transcription and activation of osteoclast marker genes. This review will briefly describe RANKL-RANK signaling pathways and key molecules critical for osteoclast differentiation.

Key Words: Osteoclast differentiation, RANK signaling, RANKL

INTRODUCTION

Bone undergoes continuous remodeling process throughout adulthood. Osteoblasts, the bone-forming cells, are derived from a mesenchymal progenitor cells, and osteoclasts, mineralized tissues-resorbing cells, are from hematopoietic progenitors of the monocyte/macrophage lineage (Suda et al., 1999; Chambers, 2000; Teitelbaum, 2000; Aubin, 2001). The functional balance between osteoblasts and osteoclasts is critical for bone homeostasis (Suda et al., 1999; Teitelbaum, 2000). The elevation of osteoclast numbers and/or activity results in bone diseases including osteoporosis, Paget's disease and rheumatoid arthritis.

To become multinucleated mature osteoclasts, mononuclear osteoclast precursors survive and fuse together by two main cytokines, macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL) (Chambers, 2000). M-CSF stimulates the proliferation and survival of osteoclast precursors via c-Fms, M-CSF receptor. The binding of RANKL to its receptor RANK provides key signals for osteoclast differentiation and bone-resorbing function as well as the survival of mature osteoclasts (Fuller et al., 1998). Co-stimulatory signaling induces Ca^{2+} oscillation for the robust production of NFATc1, which, cooperating with RANKL, finally induce complete osteoclast differentiation (Koga et al., 2004; Mócsai et al., 2004). RANKL- or RANK-deficient mice show similar osteopetrotic phenotypes due to a complete defect of osteoclasts, suggesting that RANKL-RANK signaling is essential

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for the osteoclast formation (Kong et al., 1999; Marx, 2004).

RANKL, also known as OPGL (osteoprotegerin ligand), ODF (osteoclast differentiation factor) and TRANCE (tumor necrosis factor-related activation-induced cytokine), is a type 2 membrane protein which belongs to the TNF superfamily and is synthesized by stromal cells/osteoblasts and activated T cells (Wong et al., 1997). RANKL has been shown to play important roles for lymph node formation, mammary gland development and the survival of immune cells as well as bone homeostasis in the 1990s (Anderson et al., 1997; Wong et al., 1997; Lacey et al., 1998; Naito et al., 1999; Fata et al., 2000). RANK, a type 1 transmembrane protein that belongs to the tumor necrosis factor receptor (TNFR) superfamily, is expressed primarily on monocytes/macrophages including osteoclastic precursors, activated T cells, dendritic cells, and mature osteoclasts (Anderson et al., 1997; Wong et al., 1997; Lacey et al., 1998). Osteoprotegerin (OPG) is a soluble decoy receptor for RANKL that is released from bone marrow stromal cells/osteoblasts as a soluble form (Simonet et al., 1997). OPG competes with RANK for RANKL, thereby inhibiting osteoclast differentiation and function. OPG-deficient knockout mice developed osteoporosis due to an excess of osteoclasts (Simonet at al., 1997; Bucay et al., 1998).

In this review, I will briefly describe RANK signaling pathways and key molecules inducing osteoclast differentiation. The elucidation on RANKL-RANK signaling pathways might give hints of potential drug targets for preventing bone-related diseases including osteoporosis.

TNF receptor-associated factors (TRAFs)

Stimulation of RANK by RANKL binding leads to trimerization of RANK and recruits TRAF adaptor proteins to the conserved TRAF domains within the C-terminal cytoplasmic tail of RANK (Darnay et al., 1998; Walsh and Choi, 2003). Whereas TRAF 2, 3, 5 and 6 can bind to RANK, TRAF4 was shown to be a nuclear protein so failed to interact with RANK (Darnay et al., 1998; Inoue et al., 2000; Walsh and Choi, 2003). Moreover, TRAF2, TRAF5 and TRAF6 activate transcription factors such as NF-κB and AP-1 that are required for osteoclast differentiation, however, TRAF3 serves as an inhibitor of NF-κB pathway (Kanazawa et al., 2003; Hauer et al., 2005; Kanazawa and Kudo, 2005). Among the TRAFs, TRAF6 seems to be a major adaptor protein of RANKL-RANK signaling pathway for osteoclast formation and function since the phenotype of TRAF6-deficient mice is nearly similar with the bone phenotypes of RANKL- or RANK-deficient mice, severe osteopetrosis due to impaired osteoclast differentiation or bone resorbing function (Lomaga et al., 1999; Naito et al., 1999).

However, it seems that RANKL could induce osteoclast differentiation through a TRAF6-independent signaling pathway since TRAF6-deficient hematopoietic precursors can differentiate into osteoclasts by RANKL if proper cofactors are provided, *in vitro*. Indeed, hematopoietic precursors from RANKL-, RANK-, or TRAF6-null mice can become osteoclasts *in vitro* when TNFα and cofactors such as TGF-β are supported (Kim et al., 2005). Nevertheless, RANKL-induced osteoclastogenesis is considerably reduced by TRAF6 deficiency, even cofactors are added, which implies that TRAF6 is a critical downstream mediator of RANKL-RANK signaling pathway to induce osteoclast differentiation (Kim et al., 2005).

RANK-TRAF6 interaction activates the IκB kinase (IKK) complex to stimulate Nuclear factor kappa B (NF-κB) via a signaling complex with TGFβ-activated kinase 1 (TAK1), TAK-1-binding protein 1 (TAB1) and TAB2 or atypical protein kinase C (aPKC) (Mizukami et al., 2002; Duran et al., 2004). Dominant-interfering mutant forms of TAK1 inhibit RANKL-mediated activation of both IκB kinase 1/2 (IKK1/2) and JNK1, leading to the inactivation of the NF-κB and AP-1, respectively (Mizukami et al., 2002). The interaction of TRAF6 with aPKCs is through the mediation of scaffolding protein, p62 (Duran et al., 2004).

Mitogen activated protein (MAP) kinases

Recruitment of TRAF6 to RANK activates ERK, JNK, and p38 through activation of MEK1/2, MKK7, and MKK6 in osteoclast precursors, respectively (Kashiwada et al., 1998; Matsumoto et al., 2000; Yamamoto et al., 2002; He et al., 2011). The receptor for activated C kinase 1 (RACK1) acts as a scaffold protein to link the TRAF6-TAK1 complex with MKK6, which selectively facilitates the activation of p38 during the RANKL-initiated differentiation of osteoclast precursor cells into osteoclasts (Lin et al., 2015). Moreover,

it was reported that RANK-TRAF6-Rac1-NADPH oxidase1-dependent pathway-induced reactive oxygen species production is required for MAPK activation for osteoclastogenesis (Lee et al., 2005). TRAF6 deficiency abolishes RANKL-mediated JNK and p38 MAPKs activation (Kobayashi et al., 2001). Mice with genetic deletion of *erk1* exhibited reduced osteoclast formation *in vivo*, suggesting that ERK1 plays an important role in osteoclast differentiation (He et al., 2011). ERK1/2 induces activation of their downstream targets such as c-Fos. The lack of Fos (encoding c-Fos) results in increased numbers of bone marrow macrophages with the decrease of osteoclasts (Grigoriadis et al., 1994). Osteoclast precursor cells derived from *jnk1*-lacking mice but not from *jnk2*-lacking mice exhibited reduced ability to differentiate to osteoclasts (David et al., 2002). JNK1/2 induces activation of their downstream targets such as activator protein-1 (AP-1) transcription factors (David et al., 2002).

A specific inhibitor of p38, SB203580, suppressed RANKL-mediated osteoclast differentiation in RAW 264.7 cells (Li et al., 2002). Stimulation of p38 results in the downstream activation of the transcriptional regulator mi/Mitf, which controls the expression of the genes encoding tartrate-resistant acid phosphatase (TRAP, encoded by *Acp5*) and cathepsin K (CATK), a cysteine protease (Mansky et al., 2002). Mutant osteoclasts in $Mitf^{mi/mi}$ mice are primarily mononuclear and express decreased levels of TRAP (Luchin et al., 2000; Luchin et al., 2001). Cathepsin K knockout mice develop osteopetrosis due to a deficit matrix degradation but not demineralization (Gowen et al., 1999). Similarly, mutations in the human cathepsin K gene have demonstrated an association with a rare skeletal dysplasia, pycnodysostosis (Gelb et al., 1996; Johnson et al., 1996). TRAP, an osteoclast differentiation marker, as well as cathepsin K also affect the functional activity of osteoclast by regulating bone matrix resorption and collagen turnover (Roberts et al., 2007).

Src/PI3K/Akt pathway

RANK associates with Src family kinase through interaction between TRAF6 and Cbl scaffolding proteins (Wong et al., 1999; Arron et al., 2001), activating the pro-survival factor PI3-kinase (PI3K)/Akt pathway (Wong et al., 1999). Activated PI3K generates phosphatidylinositol-(3,4,5)-phosphate (PIP3) at the plasma membrane, which leads to the recruitment of Akt/PKB via its pleckstrin homology (PH) domain and activation (Vanhaesebroeck et al., 2000). The activation of PI3K/Akt is Src-dependent because a genetic deletion of c-Src inhibits Akt activation by RANKL (Wong et al., 1999). The PI3K inhibitor LY294002 decreases osteoclast differentiation by reducing survival of osteoclast precursor cells during differentiation (Wong et al., 1999; Lee et al., 2002). Additionally, the association of the actin-binding protein gelsolin with PI3K showed that PI3K is important for the actin filament formation in osteoclasts (Chellaiah et al., 1998).

Akt induces osteoclast differentiation through regulating the GSK3β/NFATc1 signaling cascade. Akt overexpression in osteoclast precursors induces the expression and nuclear localization of NFATc1 by GSK-3β phosphorylation and inactivation (Moon et al., 2012).

Phosphatase and tensin homolog (PTEN) and SH2-containing inositol phosphatase 1 (SHIP1) negatively regulate PI3K signaling, thus reducing osteoclast differentiation (Takeshita et al., 2002; Sugatani et al., 2003). Mice lacking the SHIP-1 or tyrosine phosphatase SHP-1, both of which inhibit ITAM signaling, showed enhanced osteoclastogenesis and induced osteoporosis (Takeshita et al., 2002).

NF-κB signaling

NF-κB signaling activated by RANKL is important for osteoclast differentiation. NF-κB is including five members: c-Rel (Rel), RelA (p65), RelB, NF-κB1 (p105/p50), and NF-κB2 (p100/p52). These NF-κB proteins (p105 and p100) become shorter following post-translational processing into p50 and p52, respectively. Since p50 and p52 lack a transcription activation domain, they form dimers with Rel family members such as c-Rel (Rel), RelA (p65), RelB (Ghosh et al., 2002; Hayden et al., 2004). The NF-κB p50/p52 double-knockout (dKO) mice develop severe osteopetrosis because of a total absence of osteoclasts and show growth retardation while single knockout of p50 or p52 failed to show developmental defects (Franzoso et al., 1997; Iotsova et al., 1997). Moreover, the dKO mice showed an increase in RANK-expressing splenocytes, which suggests that p50 and p52 are necessary for osteoclastogenesis but

not for RANK-expressing progenitor formation (Xing et al., 2002). Overexpression of c-Fos rescued the defect in osteoclast formation in the absence of RANKL and dKO splenocytes treated with RANKL or TNF failed to induce c-Fos, indicating that c-Fos are downstream of NF-κB (Iotsova et al., 1997; Yamashita et al., 2007).

IκB kinase (IKK) activation by RANKL stimulation induces phosphorylation and ubiquitin-dependent proteasomal degradation of IκB. NF-κB released from the NF-κB /IκB complex translocated into the nucleus and promotes transcription of target genes (Ghosh et al., 2002; Hayden et al., 2004). NF-κB-inducing kinase (NIK) and IKKα are important for the RelB:p52 complex formation but NF-κB activation via NIK is not necessary for osteoclast formation since NIK-deficient mice failed to show osteopetrosis phenotype (Ghosh et al., 2002; Novack et al., 2003; Hayden et al., 2004).

NFATc1

NFATc1 is a master transcription factor for the terminal differentiation of osteoclasts. Activated NFATc1 undergoes nuclear translocation and activates and induces osteoclast-specific genes such as tartrate-resistant acid phosphatase (TRAP), osteoclast-associated receptor (OSCAR), cathepsin K as well as NFATcl itself (Takayanagi et al., 2002; Matsumoto et al., 2004; Asagiri et al., 2005). In addition, NFATc1 regulates cell-cell fusion of osteoclasts through up-regulation of the d2 isoform of vacuolar ATPase V0 domain (Atp6v0d2) and the dendritic cell-specific transmembrane protein (DC-STAMP) (Kim et al., 2008; Feng et al., 2009). The activation of NFATc1 is regulated by calcium/calmodulin signaling and RANK does not initiate calcium signaling directly in osteoclast precursors. Thus, the activation of NFATc1 is induced by RANKL, partially, and, for the robust activation of NFATc1, costimulatory signaling and RANKL signaling are collaborating (Takayanagi et al., 2002).

RANKL induces NFATc1 through NF-κB and c-Fos activation and a deficiency of p50/p52 or c-fos causes failure of NFATc1 induction (Li et al., 2004; Matsuo et al., 2004; Asagiri et al., 2005). NFATc1-deficient embryonic stem cells failed to differentiate into osteoclasts, and the overexpression of constitutively active NFATc1 in osteoclast precursors caused efficient osteoclast differentiation even in the absence of RANKL which suggests that NFATc1 is sufficient for osteoclastogenesis (Takayanagi et al., 2002).

CONCLUSION

The interest on the maintenance of bone homeostasis and bone remodeling occurring throughout adulthood as our life span is extended is increasing. Since 1990's, the finding of RANKL and RANK, and the studies using genetic engineered mouse models boosted significant progression in bone physiology. Especially, the importance of RANKL/RANK system in osteoclast biology has revealed critical signaling pathways and molecules regulating osteoclast differentiation. Recruitment of TRAF6 to RANK activates distinct signaling cascades and molecules as following: MAP kinases including JNK1/2, ERK1/2 and p38, Src/PI3K/Akt, Nuclear factor kappa B (NFκB) and NFATc1. Thus, although key signaling pathways and molecules involved in osteoclastogenesis have already been identified, further investigations on the molecular mechanisms specific on differentiation stages, could be of interest. Especially, more studies on detailed molecular regulatory mechanism for osteoclast fusion and bone resorbing activity would help to develop effective therapeutic drugs for bone-related diseases.

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CONFLICT OF INTEREST

The author has no conflict of interest.

REFERENCES

Anderson DM, Maraskovsky E, Billingsley WL, Dougall WC, Tometsko ME, Roux ER, Teepe MC, DuBose RF, Cosman D, Galibert L. A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. Nature.

1997. 390: 175-179.

Arron JR, Vologodskaia M, Wong BR, Naramura M, Kim N, Gu H, Choi Y. A positive regulatory role for Cbl family proteins in tumor necrosis factor-related activation-induced cytokine (trance) and CD40L-mediated Akt activation. Journal of Biological Chemistry. 2001. 276: 30011-30017.

Asagiri M, Sato K, Usami T, Ochi S, Nishina H, Yoshida H, Morita I, Wagner EF, Mak TW, Serfling E, Takayanagi H. Auto-amplification of NFATc1 expression determines its essential role in bone homeostasis. Journal of Experimental Medicine. 2005. 202: 1261-1269.

Aubin JE. Regulation of osteoblast formation and function. Reviews in Endocrine & Metabolic Disorders. 2001. 2: 81-94.

Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, Scully S, Tan HL, Xu W, Lacey DL, Boyle WJ, Simonet WS. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes & Development. 1998. 12: 1260-1268.

Chambers TJ. Regulation of the differentiation and function of osteoclasts. Journal of Pathology. 2000. 192: 4-13.

Chellaiah M, Fitzgerald C, Alvarez U, Hruska K. C-Src is required for stimulation of gelsolin-associated phosphatidylinositol 3-kinase. Journal of Biological Chemistry. 1998. 273: 11908 -11916.

Darnay BG, Haridas V, Ni J, Moore PA, Aggarwal BB. Characterization of the intracellular domain of receptor activator of NFkappaB (RANK). interaction with tumor necrosis factor receptor-associated factors and activation of NF-kappaB and c-Jun N-terminal kinase. Journal of Biological Chemistry. 1998. 273: 20551-20555.

David JP, Sabapathy K, Hoffmann O, Idarraga MH, Wagner EF. JNK1 modulates osteoclastogenesis through both c-Jun phosphorylation-dependent and -independent mechanisms. Journal of Cell Science. 2002. 115: 4317-4325.

Duran A, Serrano M, Leitges M, Flores JM, Picard S, Brown JP, Moscat J, Diaz-Meco MT. The atypical PKC-interacting protein p62 is an important mediator of RANK-activated osteoclastogenesis. Developmental Cell. 2004. 6: 303-309.

Fata JE, Kong YY, Li J, Sasaki T, Irie-Sasaki J, Moorehead RA, Elliott R, Scully S, Voura EB, Lacey DL, Boyle WJ, Khokha R, Penninger JM. The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. Cell. 2000. 103: 41-50.

Feng H, Cheng T, Steer JH, Joyce DA, Pavlos NJ, Leong C, Kular J, Liu J, Feng X, Zheng MH, Xu J. Myocyte enhancer factor2 and microphthalmia-associated transcription factor cooperate with NFATc1 to transactivate the V-ATPase d2 promoter during RANKL-induced osteoclastogenesis. Journal of Biological Chemistry. 2009. 284: 14667-14676.

Franzoso G, Carlson L, Xing L, Poljak L, Shores EW, Brown KD, Leonardi A, Tran T, Boyce BF, Siebenlist U. Requirement for NF-kappaB in osteoclast and B-cell development. Genes & Development. 1997. 11: 3482-3496.

Fuller K, Wong B, Fox S, Choi Y, Chambers TJ. TRANCE is necessary and sufficient for osteoblast-mediated activation of bone resorption in osteoclasts. Journal of Experimental Medicine. 1998. 188: 997-1001.

Gelb BD, Shi GP, Chapman HA, Desnick RJ. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. Science. 1996. 273: 1236-1238.

Ghosh S, Karin M. Missing pieces in the NF-kappaB puzzle. Cell. 2002. 109: S81-96.

Gowen M, Lazner F, Dodds R, Kapadia R, Feild J, Tavaria M, Bertoncello I, Drake F, Zavarselk S, Tellis I, Hertzog P, Debouck C, Kola I. Cathepsin K knockout mice develop osteopetrosis due to a deficit in matrix degradation but not demineralization. Journal of Bone and Mineral Research. 1999. 14: 1654-1663.

Grigoriadis AE, Wang ZQ, Cecchini MG, Hofstetter W, Felix R, Fleisch HA, Wagner EF. c-Fos: a key regulator of osteoclast macrophage lineage determination and bone remodeling. Science. 1994. 266: 443-448.

Hauer J, Puschner S, Ramakrishnan P, Simon U, Bongers M, Federle C, Engelmann H. TNF receptor (TNFR)-associated factor (TRAF) 3 serves as an inhibitor of TRAF2/5-mediated activation of the noncanonical NF-kappaB pathway by TRAF-binding TNFRs. Proceedings of the National Academy of Sciences of the United States of America. 2005. 102: 2874 -2879.

Hayden MS, Ghosh S. Signaling to NF-kappa B. Genes & Development. 2004. 18: 2195-2224.

He Y, Staser K, Rhodes SD, Liu Y, Wu X, Park SJ, Yuan J, Yang X, Li X, Jiang L, Chen S, Yang FC. Erk1 positively regulates osteoclast differentiation and bone resorptive activity. PLOS One. 2011. 6: e24780.

Inoue JI, Ishida T, Tsukamoto N, Kobayashi N, Naito A, Azuma S, Yamamoto T. Tumor necrosis factor receptor-associated factor (TRAF) family: adapter proteins that mediate cytokine signaling. Experimental Cell Research. 2000. 254: 14-24.

Iotsova V, Caamaño J, Loy J, Yang Y, Lewin A, Bravo R. Osteo-

petrosis in mice lacking NF-kappaB1 and NF-kappaB2. Nature Medicine. 1997. 3: 1285-1289.

Johnson MR, Polymeropoulos MH, Vos HL, Ortiz de Luna RI, Francomano CA. A nonsense mutation in the cathepsin K gene observed in a family with pycnodysostosis. Genome Research. 1996. 6: 1050-1055.

Kanazawa K, Kudo A. TRAF2 is essential for TNF-alpha-induced osteoclastogenesis. Journal of Bone and Mineral Research. 2005. 20: 840-847.

Kanazawa K, Azuma Y, Nakano H, Kudo A. TRAF5 functions in both RANKL- and TNF alpha-induced osteoclastogenesis. Journal of Bone and Mineral Research. 2003. 18: 443-450.

Kashiwada M, Shirakata Y, Inoue JI, Nakano H, Okazaki K, Okumura K, Yamamoto T, Nagaoka H, Takemori T. Tumor necrosis factor receptor-associated factor 6 (TRAF6) stimulates extracellular signal-regulated kinase (ERK) activity in CD40 signaling along a ras-independent pathway. Journal of Experimental Medicine. 1998. 187: 237-244.

Kim N, Kadono Y, Takami M, Lee J, Lee SH, Okada F, Kim JH, Kobayashi T, Odgren PR, Nakano H, Yeh WC, Lee SK, Lorenzo JA, Choi Y. Osteoclast differentiation independent of the TRANCE-RANK-TRAF6 axis. Journal of Experimental Medicine. 2005. 202: 589-595.

Kim K, Lee SH, Ha KJ, Choi Y, Kim N. NFATc1 induces osteoclast fusion via up-regulation of Atp6v0d2 and the dendritic cell-specific transmembrane protein (DC-STAMP). Molecular Endocrinology. 2008. 22: 176-185.

Kobayashi N, Kadono Y, Naito A, Matsumoto K, Yamamoto T, Tanaka S, Inoue J. Segregation of TRAF6-mediated signaling pathways clarifies its role in osteoclastogenesis. The EMBO Journal. 2001. 20: 1271-1280.

Koga T, Inui M, Inoue K, Kim S, Suematsu A, Kobayashi E, Iwata T, Ohnishi H, Matozaki T, Kodama T, Taniguchi T, Takayanagi H, Takai T. Costimulatory signals mediated by the ITAM motif cooperate with RANKL for bone homeostasis. Nature. 2004. 428: 758-763.

Kong YY, Yoshida H, Sarosi I, Tan HL, Timms E, Capparelli C, Morony S, Oliveira-dos-Santos AJ, Van G, Itie A, Khoo W, Wakeham A, Dunstan CR, Lacey DL, Mak TW, Boyle WJ, Penninger JM. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature. 1999. 397: 315-323.

Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, Elliott R, Colombero A, Elliott G, Scully S, Hsu H, Sullivan J, Hawkins N, Davy E, Capparelli C, Eli A, Qian YX, Kaufman S, Sarosi I, Shalhoub V, Senaldi G, Guo J, Delaney J, Boyle WJ. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998. 93: 165-176.

Lee NK, Choi YG, Baik JY, Han SY, Jeong DW, Bae YS, Kim N, Lee SY. A crucial role for reactive oxygen species in RANKL-induced osteoclast differentiation. Blood. 2005. 106: 852-859.

Lee SE, Woo KM, Kim SY, Kim HM, Kwack K, Lee ZH, Kim HH. The phosphatidylinositol 3-kinase, p38, and extracellular signal-regulated kinase pathways are involved in osteoclast differentiation. Bone. 2002. 30: 71-77.

Li F, Matsuo K, Xing L, Boyce BF. Over-expression of activated NFATc1 plus RANKL rescues the osteoclastogenesis defect of NF-κB p50/p52 double knockout splenocytes. Journal of Bone and Mineral Research. 2004. 19: S2.

Li X, Udagawa N, Itoh K, Suda K, Murase Y, Nishihara T, Suda T, Takahashi N. p38 MAPK-mediated signals are required for inducing osteoclast differentiation but not for osteoclast function. Endocrinology. 2002. 143: 3105-3113.

Lin J, Lee D, Choi Y, Lee SY. The scaffold protein RACK1 mediates the RANKL-dependent activation of p38 MAPK in osteoclast precursors. Science Signaling. 2015. 8: ra54.

Lomaga MA, Yeh WC, Sarosi I, Duncan GS, Furlonger C, Ho A, Morony S, Capparelli C, Van G, Kaufman S, van der Heiden A, Itie A, Wakeham A, Khoo W, Sasaki T, Cao Z, Penninger JM, Paige CJ, Lacey DL, Dunstan CR, Boyle WJ, Goeddel DV, Mak TW. TRAF6 deficiency results in osteopetrosis and defective interleukin-1, CD40, and LPS signaling. Genes & Development. 1999. 13: 1015-1024.

Luchin A, Purdom G, Murphy K, Clark MY, Angel N, Cassady AI, Hume DA, Ostrowski MC. The microphthalmia transcription factor regulates expression of the tartrate-resistant acid phosphatase gene during terminal differentiation of osteoclasts. Journal of Bone and Mineral Research. 2000. 15: 451-460.

Luchin A, Suchting S, Merson T, Rosol TJ, Hume DA, Cassady AI, Ostrowski MC. Genetic and physical interactions between microphthalmia transcription factor and PU.1 are necessary for osteoclast gene expression and differentiation. Journal of Biological Chemistry. 2001. 276: 36703-36710.

Mansky KC, Sankar U, Han J, Ostrowski MC. Microphthalmia transcription factor is a target of the p38 MAPK pathway in response to receptor activator of NF-kappa B ligand signaling. Journal of Biological Chemistry. 2002. 277: 11077-11083.

Marx J. Coming to grips with bone loss. Science. 2004. 305: 1420-1422.

Matsumoto M, Kogawa M, Wada S, Takayanagi H, Tsujimoto M,

Katayama S, Hisatake K, Nogi Y. Essential role of p38 mitogen-activated protein kinase in cathepsin K gene expression during osteoclastogenesis through association of NFATc1 and PU.1. Journal of Biological Chemistry. 2004. 279: 45969 -45979.

Matsumoto M, Sudo T, Saito T, Osada H, Tsujimoto M. Involvement of p38 mitogen-activated protein kinase signaling pathway in osteoclastogenesis mediated by receptor activator of NF-kappa B ligand (RANKL). Journal of Biological Chemistry. 2000. 275: 31155-31161.

Matsuo K, Galson DL, Zhao C, Peng L, Laplace C, Wang KZ, Bachler MA, Amano H, Aburatani H, Ishikawa H, Wagner EF. Nuclear factor of activated T-cells (NFAT) rescues osteoclastogenesis in precursors lacking c-Fos. Journal of Biological Chemistry. 2004. 279: 26475-26480.

Mizukami J, Takaesu G, Akatsuka H, Sakurai H, Ninomiya-Tsuji J, Matsumoto K, Sakurai N. Receptor activator of NF-kappaB ligand (RANKL) activates TAK1 mitogen-activated protein kinase kinase kinase through a signaling complex containing RANK, TAB2, and TRAF6. Molecular and Cellular Biology. 2002. 22: 992-1000.

Mócsai A, Humphrey MB, Van Ziffle JA, Hu Y, Burghardt A, Spusta SC, Majumdar S, Lanier LL, Lowell CA, Nakamura MC. The immunomodulatory adapter proteins DAP12 and Fc receptor gamma-chain (FcRgamma) regulate development of functional osteoclasts through the Syk tyrosine kinase. Proceedings of the National Academy of Sciences of the United States of America. 2004. 101: 6158-6163.

Moon JB, Kim JH, Kim K, Youn BU, Ko A, Lee SY, Kim N. Akt induces osteoclast differentiation through regulating the GSK3β /NFATc1 signaling cascade. Journal of Immunology. 2012. 188: 163-169.

Naito A, Azuma S, Tanaka S, Miyazaki T, Takaki S, Takatsu K, Nakao K, Nakamura K, Katsuki M, Yamamoto T, Inoue J. Severe osteopetrosis, defective interleukin-1 signaling and lymph node organogenesis in TRAF6-deficient mice. Genes to Cells. 1999. 4: 353-362.

Novack DV, Yin L, Hagen-Stapleton A, Schreiber RD, Goeddel DV, Ross FP, Teitelbaum SL. The IkappaB function of NF-kappaB2 p100 controls stimulated osteoclastogenesis. Journal of Experimental Medicine. 2003. 198: 771-781.

Roberts HC, Knott L, Avery NC, Cox TM, Evans MJ, Hayman AR. Altered collagen in tartrate-resistant acid phosphatase (TRAP)-deficient mice: a role for TRAP in bone collagen metabolism. Calcified Tissue International. 2007. 80: 400-410.

Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Luthy R, Nguyen HQ, Wooden S, Bennett L, Boone T, Shimamoto G, DeRose M, Elliott R, Colombero A, Tan HL, Trail G, Sullivan J, Davy E, Bucay N, Renshaw-Gegg L, Hughes TM, Hill D, Pattison W, Campbell P, Sander S, Van G, Tarpley J, Derby P, Lee R, Boyle WJ. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell. 1997. 89: 309-319.

Suda T, Takahashi N, Udagawa N, Jimi E, Gillespie MT, Martin TJ. Modulation of osteoclast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families. Endocrine Review. 1999. 20: 345-357.

Sugatani T, Alvarez U, Hruska KA. PTEN regulates RANKL- and osteopontin-stimulated signal transduction during osteoclast differentiation and cell motility. Journal of Biological Chemistry. 2003. 278: 5001-5008.

Takayanagi H, Kim S, Koga T, Nishina H, Isshiki M, Yoshida H, Saiura A, Isobe M, Yokochi T, Inoue J, Wagner EF, Mak TW, Kodama T, Taniguchi T. Induction and activation of the transcription factor NFATc1 (NFAT2) integrate RANKL signaling in terminal differentiation of osteoclasts. Developmental Cell. 2002. 3: 889-901.

Takeshita S, Namba N, Zhao JJ, Jiang Y, Genant HK, Silva MJ, Brodt MD, Helgason CD, Kalesnikoff J, Rauh MJ, Humphries RK, Krystal G, Teitelbaum SL, Ross FP. SHIP-deficient mice are severely osteoporotic due to increased numbers of hyper-resorptive osteoclasts. Nature Medicine. 2002. 8: 943-949.

Teitelbaum SL. Bone resorption by osteoclasts. Science. 2000. 289: 1504-1508.

Vanhaesebroeck B, Alessi DR. The PI3K-PDK1 connection: more than just a road to PKB. Biochemistry Journal. 2000. 346: 561 -576.

Walsh MC, Choi Y. Biology of the TRANCE axis. Cytokine & Growth Factor Reviews. 2003. 14: 251-263.

Wong BR, Besser D, Kim N, Arron JR, Vologodskaia M, Hanafusa H, Choi Y. TRANCE, a TNF family member, activates Akt/ PKB through a signaling complex involving TRAF6 and c-Src. Molecular Cell. 1999. 4: 1041-1049.

Wong BR, Josien R, Lee SY, Sauter B, Li HL, Steinman RM, Choi Y. TRANCE (tumor necrosis factor [TNF]-related activation-induced cytokine), a new TNF family member predominantly expressed in T cells, is a dendritic cell-specific survival factor. Journal of Experimental Medicine. 1997. 186: 2075-2080.

Xing L, Bushnell TP, Carlson L, Tai Z, Tondravi M, Siebenlist U, Young F, Boyce BF. NF-kappaB p50 and p52 expression is

not required for RANK expressing osteoclast progenitor formation but is essential for RANK- and cytokine mediated osteoclastogenesis. Journal of Bone and Mineral Research. 2002. 17. 1200-1210.

Yamamoto A, Miyazaki T, Kadono Y, Takayanagi H, Miura T, Nishina H, Katada T, Wakabayashi K, Oda H, Nakamura K, Tanaka S. Possible involvement of IkappaB kinase 2 and MKK7 in osteoclastogenesis induced by receptor activator of nuclear factor kappaB ligand. Journal of Bone and Mineral Research. 2002. 17: 612-621.

Yamashita T, Yao Z, Li F, Zhang Q, Badell IR, Schwarz EM, Takeshita S, Wagner EF, Noda M, Matsuo K, Xing L, Boyce BF. NF-kappaB p50 and p52 regulate receptor activator of NF-kappaB ligand (RANKL) and tumor necrosis factor-induced osteoclast precursor differentiation by activating c-Fos and NFATc1. Journal of Biological Chemistry. 2007. 282: 18245-18253.

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