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## IMMUNOPATHOLOGY IN OSTEOPOROSIS

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### Abstract:

Osteoporosis is a bone-damaging metabolic disorder. Reduced bone matrix causes damage to bone tissue microarchitecture due to aberrant bone turnover during the remodeling process, resulting in decreased bone mass and strength. Excess bone resorption and osteoporosis result from an imbalance of activity between osteoclasts and osteoblasts. Osteoporosis has a significant impact on a person's ability to carry out daily tasks. Falls and fracture complications are also more frequent. Increased osteoclast activity could be caused by a lack of estrogen, cytokine factors, or bone pressure, according to the hypothesis. The activity of pro-inflammatory mediators is inversely related to estrogen levels. Estrogen deficiency causes the release of cytokines and a decrease in the performance of T cells that support osteoclastogenesis, as well as an increase in B cells, pro-inflammatory, and pro-osteoclastogenesis interleukins. As a result, RANKL expression rises, and osteoclast proliferation occurs. TNF alpha is involved in the osteoclastogenesis stage and interacts with RANKL to activate osteoclasts indirectly. Other cytokines, such as IL-1, IL-6, and IL-7, can also promote osteoclastogenesis. Interferon-gamma, IL-4, IL-10, and IL-12 all suppress it. Understanding the pathophysiology of osteoporosis can lead to advances in treatment and prevention, lowering morbidity, and mortality in patients.

**Keywords:** bone remodeling, inflammatory mediators, osteoblasts, osteoclasts, osteoimmunology, osteoporosis

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### INTRODUCTION

Osteoporosis is a metabolic disease characterized by a decreased bone matrix, which causes damage to the microarchitecture of bone tissue due to aberrant bone turnover during the remodeling process.<sup>1</sup> As a result, bone mass and strength weaken. Since the bones become easily fractured, this condition might lead to complications. The

processes of bone formation by osteoblasts and resorption by osteoclasts occur continuously throughout human life. If there is an imbalance in activity between the two types of cells, where osteoclasts are more dominant than osteoblasts, bone turnover abnormalities develop, specifically the process of bone resorption is greater than the process of



bone formation, leading to osteoporosis.<sup>2,3</sup>

The relationship between bone and the immunological system is known as osteoimmunology.<sup>4</sup> Normal immune cell activity results in balanced mineralization and bone resorption, both of which are played by osteoblasts and osteoclasts.<sup>5</sup> The immune system can act as a protector for the body because it can differentiate between self-cells and foreign components. However, in certain circumstances the immune system is unable to distinguish and recognize foreign components, resulting in autoimmune diseases. Where the body's immune cells attack their cells because they are misinterpreted as dangerous foreign objects. In inflammatory and autoimmune cases, RANKL and inflammatory cytokines are formed due to the activation of T cell products that can induce RANKL expression in osteoblasts.<sup>6</sup> Several T-cell-derived cytokines, such as IL-12 and IL-18, can intermingle with the RANK signaling pathway, osteoclastogenesis, and osteoclast functions.<sup>7</sup>

Osteoporosis is divided into several classifications based on the cause: primary osteoporosis and secondary osteoporosis. Primary osteoporosis is divided into 2 types: primary osteoporosis type 1 occurs in post-menopause women, and type 2 osteoporosis occurs in elderly people (>70 years).<sup>8</sup> While secondary osteoporosis occurs due to other underlying diseases, for example, osteoporosis that occurs in patients with bone TB, osteomalacia, chronic rheumatoid arthritis, in addition to long-term steroid use, or hyperthyroidism.<sup>9,10</sup> Osteoporosis greatly impacts a person's ability to carry out daily activities. The risk of falls and fracture complications also increases. This will increase morbidity and mortality. Understanding the pathophysiology can

be the basis for advances in therapy and prevention of osteoporosis.<sup>11</sup>

## DISCUSSION

Several factors can contribute to increased osteoclast activity, which leads to excessive bone resorption. According to the theory, it could be linked to a lack of estrogen, cytokine factors, and the burden on the bones. Osteocytes are the most dominant bone-forming cells. Only 10% of bone components are not osteocytes.<sup>12</sup> The osteocytes produce sclerostin, which regulates bone matrix mineralization to prevent excessive bone formation by inhibiting canonical Wnt signaling so that it fails to increase the transcription of osteogenic genes during bone formation.<sup>13,14</sup> In the cytosol, osteoblasts have 2 estrogen receptors: alpha and beta estrogen receptors. However, in its work, the expression of beta receptors is 10 times stronger than that of alpha estrogen receptors. The normal bone should have a balanced expression of forming cells (osteoblasts) and absorbing cells (osteoclasts).<sup>15</sup>

The estrogen hormone in bone cells plays a role in reducing various proinflammatory cytokines from bone marrow stromal cells and mononuclear cells that can lead to increased differentiation and maturation of osteoclasts, such as IL-1, IL-6, and TNF- $\alpha$ , as well as triggering osteoblasts to reduce TGF- $\beta$  release. Postmenopausal women experience a decrease in estrogen levels so that the work of osteoclasts increases both, directly and indirectly, eventually increasing bone resorption.<sup>16</sup> Estrogen deficiency will cause the release of cytokines that support the formation of osteoclasts. When estrogen is deficient, FSH levels are elevated, and osteoclasts and their precursors have FSH receptors. This condition results in increased osteoclast activity and bone remodeling activity in conditions of estrogen



deficiency, one of which is menopause.<sup>17</sup> One type of osteoporosis is primary type 1, which occurs after menopause. Scientists have determined that estrogen replacement therapy can be used to treat osteoporosis in postmenopausal women.<sup>18</sup> Because estrogen can stimulate the expression of osteoprotegerin (OPG) and Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) in osteoblasts and stromal cells.

OPG is an inhibitor of osteoclastogenesis by inhibiting the binding between the Receptor Activator of Nuclear Factor Kappa- $\beta$  ligand (RANKL) and Receptor Activator of Nuclear Factor Kappa- $\beta$  (RANK).<sup>19</sup> RANKL is one of the TNF- $\alpha$  cytokines, it is binding to RANK will facilitate the occurrence of bone destruction.<sup>20</sup> RANKL and RANK are regulators of bone remodeling and importance in osteoclast development and activation. Interestingly, the RANKL/RANK interaction also regulates T cell, dendritic cell survival, and lymph node formation.<sup>21,22</sup> RANKL binds to the RANK expression on signal transduction activation of hematopoietic progenitors that cause osteoclasts differentiation. RANKL stimulates bone resorption activity in mature osteoclasts via RANK. When RANK is activated, the signal will be sent into the cell via Tumor Necrosis Factor Receptor-Associated Factors (TRAFs) receptors, especially TRAF6. RANK is important in the activation and differentiation of osteoclasts for bone resorption, and also acts as a link in the NF- $\kappa$ B, JNK/SAPK, p38, and Akt/PKB pathways.<sup>23</sup>

Osteoprotegerin (OPG) is an osteoclastogenesis inhibitory factor, that functions as a RANKL receptor that binds to RANK.<sup>24</sup> When the binding of RANK and RANKL is inhibited by OPG, there is no osteoclast formation and excessive bone resorption. OPG activity can increase triggered by IL-4, IL-10, IL-13, IL-18, and

estrogen.<sup>25</sup> So that one of the mechanisms of osteoporosis in menopausal women is due to decreased estrogen and reduced OPG activity. Thus, the correlation between RANKL, RANK, and OPG makes a molecular link between bone remodeling, the immune system, and inflammation.<sup>25</sup>

Meanwhile, TGF- $\beta$  is released from bone during active bone resorption as a feedback mechanism by upregulating OPG levels. TGF- $\beta$  plays a role in the proliferation of osteoblasts and inhibits their apoptosis, on the other hand, osteoclast apoptosis increases, and excess bone resorption can be prevented.<sup>26</sup>

Estrogen also plays a role in regulating activity and increasing the number of T cells.<sup>27</sup> T cells maintain immune homeostasis, inhibit inflammation, and inhibit monocyte differentiation into osteoclasts.<sup>28</sup> Studies in mice with overexpression of T cells showed a high bone mass index, due to inhibition of osteoclasts activity in bone resorption.<sup>29</sup> Therefore, decreased estrogen levels in postmenopausal women cause decreased T-cell performance and increased osteoclasts, resulting in osteoporosis.<sup>18</sup>

In summary, a person who suffers from estrogen insufficiency will experience an increase in B cells, T cells, as well as pro-inflammatory and pro-osteoclastogenic interleukins. As a result, RANKL expression rises and osteoclast proliferation occurs.<sup>30</sup>

The performance of osteoblasts in bone formation is also enhanced by parathyroid hormone and vitamin D.<sup>31</sup> Vitamin D is one of the calcitropic factors (in addition to PGE2, IL-1, IL-11, TNF- and glucocorticoid factors) that induce RANKL expression in osteoblasts.<sup>32</sup> Vitamin D has anti-inflammatory properties and may influence the regulation of immune function, the proliferation, and differentiation of many cell types.<sup>33</sup> Studies revealed that the effects of vitamin D





resulted in suppression of inflammation-related genes expression, including decreased TNF- $\alpha$  gene expression induced by intense exercise.<sup>34,35</sup>

Production of IL-1, IL-6, and/or TNF- $\alpha$  has shown a positive correlation with bone resorption or bone loss.<sup>36</sup> TNF- $\alpha$ , IL-1, IL-6, IL-23, IL-27, and all of the pro-inflammatory mediators may worsen the progression of osteoporosis by destroying cartilage and bone due to increased osteoclast activity.<sup>37</sup> These mediators are activated by macrophages. TNF  $\alpha$  specifically plays a role in the osteoclastogenesis stage and indirectly engages with RANKL to trigger osteoclast activation.<sup>38</sup> However, this effect can be inhibited by IL-18 which is also secreted by macrophages, it also regulates Th1 and IFN- $\gamma$ .<sup>39</sup> Interferon (IFN)- $\gamma$  secretion T-cell-dependent enhances bone resorption, further supporting T-cell-dependent co-secretion of TNF- $\alpha$  and RANKL under estrogen deficiency and infection. This explains the pathophysiology of osteoporosis in association with chronic inflammatory disorders such as periodontitis in postmenopausal women. Osteoclasts are also activated by IL-23.<sup>40</sup>

Expression of RANKL in osteoblasts is also increased due to the production of cytokines that are activated by T cells.<sup>41</sup> Activation of T cells directly expresses and produces RANKL, induces osteoclast formation, and activates via specific receptors. There are several mechanisms and interactions by which cytokines regulate bone resorption. IL-6 contributes to the upregulation of RANKL in osteoblast cells. IL-1 and TNF- $\alpha$  may also not promote osteoclast development, but they stimulate mature osteoclasts to cycle through the resorption cycle by modulating RANKL activity.<sup>42,43</sup> IL-1 is widely involved in bone metabolism as well as an osteoblast activator function. IL-1 and IL-6 also directly increase osteoclast activity by a RANKL-independent

mechanism. These molecules directly extend the lifespan of osteoclasts to inhibit osteoclast apoptosis. TNF- $\alpha$  and IL-1 inhibit collagen synthesis in osteoblasts and promote extracellular matrix degradation.<sup>44</sup>

RANKL activation will decrease due to suppression by IL-27 which is also able to increase Egr-2 expression to prevent osteoblast apoptosis.<sup>45</sup> The function of RANKL can be played by IL-1 directly, or IL-1 indirectly triggers RANKL expression. Therefore, IL-1 is known as an osteoclast activating factor.<sup>46</sup> But on the other hand, IL-1 also regulates the release of OPG which inhibits bone resorption by preventing the binding of RANKL to RANK, and in turn stimulates apoptosis of osteoclast cells.<sup>47</sup>

In malignancy, high levels of IL-1 can be a marker of bone metastases. Because IL-1 increases the formation of new blood vessels and stimulates more pro-inflammatory cytokines that support cancer cell growth and invasion into bone.<sup>48</sup> The process of osteoclastogenesis is inhibited by interferon-gamma, IL-4, IL-10, and IL-12. In contrast, osteoclastogenesis will be stimulated by the presence of Tumor Necrosis Factor (TNF), IL-1, IL-6, and IL-7.<sup>49</sup> Estrogen levels are inversely proportional to the activity of pro-inflammatory mediators.<sup>50</sup>

## Conclusion

Bone and the immune system are two interrelated organ systems called osteoimmunology. In the pathophysiology of osteoporosis, the immune system is involved in a complex manner. The role of pro-inflammatory cytokines, hormones, and other factors greatly influences the balance of bone formation and resorption carried out by osteoblasts and osteoclasts. Understanding the pathophysiology of osteoporosis can lead to advances in treatment and prevention, lowering



morbidity, and mortality of osteoporosis patients.

## References

- 1) Zhang T, Liu P, Zhang Y, Wang W, Lu Y, Xi M, Duan S, Guan F. Combining information from multiple bone turnover markers as diagnostic indices for osteoporosis using support vector machines. *Biomarkers*. 2019 Feb 17;24(2):120-6.
- 2) De Martinis M, Ginaldi L, Sirufo MM, Pioggia G, Calapai G, Gangemi S, Mannucci C. Alarmins in osteoporosis, RAGE, IL-1, and IL-33 pathways: a literature review. *Medicina*. 2020 Mar;56(3):138.
- 3) Calleja-Agius J, Brincat M. Menopause-Related Changes in the Musculoskeletal System, Cartilages and Joints. In *Frontiers in Gynecological Endocrinology 2014* (pp. 201-205). Springer, Cham.
- 4) Rabjohns, Emily M., Katlyn Hurst, Arin Ghosh, Maria C. Cuellar, Rishi R. Rampersad, and Teresa K. Tarrant. "Paget's Disease of Bone: Osteoimmunology and Osteoclast Pathology." *Current allergy and asthma reports* 21, no. 4 (2021): 1-12
- 5) Mi B, Chen L, Xiong Y, Yang Y, Panayi AC, Xue H, Hu Y, Yan C, Hu L, Xie X, Lin Z. Osteoblast/Osteoclast and Immune Cocktail Therapy of an Exosome/Drug Delivery Multifunctional Hydrogel Accelerates Fracture Repair. *ACS nano*. 2022
- 6) Wijaksana IK, Prahasanti C, Bargowo L, Sukarsono RM, Krismariono A. OPG and RANKL Expression in Osteoblast Culture after Application of Osphronemus Gourami Fish Scale Collagen Peptide. *Journal of International Dental and Medical Research*. 2021 May 1;14(2):618-22
- 7) Holliday LS, Patel SS, Rody Jr WJ. RANKL and RANK in extracellular vesicles: Surprising new players in bone remodeling. *Extracellular vesicles and circulating nucleic acids*. 2021;2:18.
- 8) Manchireddy B, Marte MG, Adler RA. Osteoporosis in Men. In *Osteoporosis 2021* (pp. 83-90). Springer, Cham.
- 9) De Martinis M, Allegra A, Sirufo MM, Tonacci A, Pioggia G, Raggiunti M, Ginaldi L, Gangemi S. Vitamin D Deficiency, Osteoporosis and Effect on Autoimmune Diseases and Hematopoiesis: A Review. *International Journal of Molecular Sciences*. 2021 Jan;22(16):8855.
- 10) El-Gazzar A, Högl W. Mechanisms of bone fragility: from osteogenesis imperfecta to secondary osteoporosis. *International Journal of Molecular Sciences*. 2021 Jan;22(2):625.
- 11) Migliorini F, Colarossi G, Baroncini A, Eschweiler J, Tingart M, Maffulli N. Pharmacological Management of Postmenopausal Osteoporosis: a Level I Evidence Based-Expert Opinion. *Expert Review of Clinical Pharmacology*. 2021 Jan 2;14(1):105-19
- 12) Wang K, Ren Y, Lin S, Jing Y, Ma C, Wang J, Yuan XB, Han X, Zhao H, Wang Z, Zheng M. Osteocytes but not osteoblasts directly build mineralized bone structures. *International journal of biological sciences*. 2021;17(10):2430.
- 13) Langdahl BL, Hofbauer LC, Forfar JC. Cardiovascular safety and sclerostin Inhibition. *The Journal of Clinical Endocrinology & Metabolism*. 2021 Jul;106(7):1845-53.
- 14) Dirkes RK, Winn NC, Jurrissen TJ, Lubahn DB, Vieira-Potter VJ, Padilla J, Hinton PS. Voluntary wheel running partially compensates for the effects of global estrogen receptor- $\alpha$  knockout on cortical bone in young male mice. *International Journal of*



- Molecular Sciences. 2021 Jan;22(4):1734.
- 15) Yang DH, Yang MY. The role of macrophage in the pathogenesis of osteoporosis. *International journal of molecular sciences*. 2019 Jan;20(9):2093.
- 16) Li H, Xu J, Li X, Hu Y, Liao Y, Zhou W, Song Z. Anti-inflammatory activity of psoralen in human periodontal ligament cells via estrogen receptor signaling pathway. *Scientific reports*. 2021 Apr 22;11(1):1-2.
- 17) Chin KY. The relationship between follicle-stimulating hormone and bone health: Alternative explanation for bone loss beyond oestrogen?. *International journal of medical sciences*. 2018;15(12):1373.
- 18) Khosla S, Pacifici R. Estrogen deficiency and the pathogenesis of osteoporosis. In Marcus and Feldman's Osteoporosis 2021 Jan 1 (pp. 773-797). Academic Press.
- 19) Li X, Cui L, Chen W, Fang Y, Shen G, Li Z, Zhang B, Wu L. QiangGuYin Modulates the OPG/RANKL/RANK Pathway by Increasing Secretin Levels during Treatment of Primary Type I Osteoporosis. *Evidence-Based Complementary and Alternative Medicine*. 2021 Oct 31;2021.
- 20) Yao Z, Getting SJ, Locke IC. Regulation of TNF-Induced Osteoclast Differentiation. *Cells*. 2021 Dec 31;11(1):132.
- 21) Walsh MC, Choi Y. Regulation of T cell-associated tissues and T cell activation by RANKL-RANK-OPG. *Journal of Bone and Mineral Metabolism*. 2021 Jan;39(1):54-63.
- 22) Honma M, Ikebuchi Y, Suzuki H. RANKL as a key figure in bridging between the bone and immune system: Its physiological functions and potential as a pharmacological target. *Pharmacology & therapeutics*. 2021 Feb 1;218:107682.
- 23) Munmun F, Witt-Enderby PA. Melatonin effects on bone: implications for use as a therapy for managing bone loss. *Journal of Pineal Research*. 2021 Aug;71(1):e12749.
- 24) Udagawa N, Koide M, Nakamura M, Nakamichi Y, Yamashita T, Uehara S, Kobayashi Y, Furuya Y, Yasuda H, Fukuda C, Tsuda E. Osteoclast differentiation by RANKL and OPG signaling pathways. *Journal of bone and mineral metabolism*. 2021 Jan;39(1):19-26.
- 25) Gnoni A, Brunetti O, Longo V, Calabrese A, Argentiero AL, Calbi R, Antonio GS, Licchetta A. Immune system and bone microenvironment: Rationale for targeted cancer therapies. *Oncotarget*. 2020 Jan 28;11(4):480.
- 26) Kasagi, S.; Chen, W. Tgf-beta1 on osteoimmunology and the bone component cells. *Cell Biosci*. 2013, 3, 4. [CrossRef] [PubMed], 6-8 *Int. J. Mol. Sci*. 2019, 20, 2093; doi:10.3390/ijms20092093
- 27) Induction of regulatory T cells by physiological level estrogen. Ping Tai, Junpeng Wang, Huali Jin, Xiaoming Song, Jun Yan, Youmin Kang, Lin Zhao, Xiaojin An, Xiaogang Du, Xiufen Chen, Songbo Wang, Guoliang Xia
- 28) Zhu X, Zeng Z, Qiu D, Chen J. Vγ9Vδ2 T cells inhibit immature dendritic cell transdifferentiation into osteoclasts through downregulation of RANK, c-Fos and ATP6V0D2. *International Journal of Molecular Medicine*. 2018 Oct 1;42(4):2071-9.
- 29) Zaiss MM, Sarter K, Hess A, et al. Increased bone density and resistance to ovariectomy-induced bone loss in FoxP3- transgenic mice based on impaired osteoclast differentiation. *Arthritis Rheum* 2010;62(8):2328-38
- 30) Zha L, He L, Liang Y, Qin H, Yu B, Chang L, Xue L. TNF-α contributes to



- postmenopausal osteoporosis by synergistically promoting RANKL-induced osteoclast formation. *Biomedicine & Pharmacotherapy*. 2018 Jun 1;102:369-74.
- 31) Bhattarai HK, Shrestha S, Rokka K, Shakya R. Vitamin D, calcium, parathyroid hormone, and sex steroids in bone health and effects of aging. *Journal of osteoporosis*. 2020 Jun 17;2020.
  - 32) L Bishop E, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. *JBMR plus*. 2021 Jan;5(1):e10405.
  - 33) Lin KM, Lu CL, Hung KC, Wu PC, Pan CF, Wu CJ, Syu RS, Chen JS, Hsiao PJ, Lu KC. The paradoxical role of uric acid in osteoporosis. *Nutrients*. 2019 Sep;11(9):2111.
  - 34) Caballero-García A, Córdova-Martínez A, Vicente-Salar N, Roche E, Pérez-Valdecantos D. Vitamin D, Its role in recovery after muscular damage following exercise. *Nutrients*. 2021 Jul;13(7):2336.
  - 35) Córdova, A.; Sureda, A.; Pons, A.; Alvarez-Mon, M. Modulation of TNF- $\alpha$ , TNF- $\alpha$  Receptors and IL-6 after Treatment with AM3 in Professional Cyclists. *J. Sports Med. Phys. Fitness* 2015, 55, 345–351.
  - 36) Jeedigunta Y, Sultana S, Kalashikam RR, Manchala R. Systemic Inflammation: A Risk Factor for Osteoporosis in Pre-and Postmenopausal Women. *Journal of Womens Health and Development*. 2020;3(4):423-31.
  - 37) Jung, Y.K.; Kang, Y.M.; Han, S. Osteoclasts in the inflammatory arthritis: Implications for pathologic osteolysis. *Immune Netw*. 2019, 19, e2
  - 38) Luo G, Li F, Li X, Wang ZG, Zhang B. TNF- $\alpha$  and RANKL promote osteoclastogenesis by upregulating RANK via the NF- $\kappa$ B pathway. *Molecular medicine reports*. 2018 May 1;17(5):6605-11.
  - 39) Sims NA, Green JR, Glatt M, Schlicht S, Martin TJ, Gillespie MT, Romas E. Targeting osteoclasts with zoledronic acid prevents bone destruction in collagen-induced arthritis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 2004 Jul;50(7):2338-46.
  - 40) Yuan N, Yu G, Liu D, Wang X, Zhao L. An emerging role of interleukin-23 in rheumatoid arthritis. *Immunopharmacology and immunotoxicology*. 2019 Mar 4;41(2):185-91.
  - 41) Wu L, Su Y, Lin F, Zhu S, Wang J, Hou Y, Du J, Liu Y, Guo L. MicroRNA-21 promotes orthodontic tooth movement by modulating the RANKL/OPG balance in T cells. *Oral Diseases*. 2020 Mar;26(2):370-80.
  - 42) Wang T, He C. TNF- $\alpha$  and IL-6: the link between immune and bone system. *Current Drug Targets*. 2020 Mar 1;21(3):213-27.
  - 43) Yao Z, Getting SJ, Locke IC. Regulation of TNF-Induced Osteoclast Differentiation. *Cells*. 2021 Dec 31;11(1):132.
  - 44) Chen YP, Chu YL, Tsuang YH, Wu Y, Kuo CY, Kuo YJ. Anti-inflammatory effects of adenine enhance osteogenesis in the osteoblast-like mg-63 cells. *Life*. 2020 Jul;10(7):116.
  - 45) Shukla P, Mansoori MN, Kakaji M, Shukla M, Gupta SK, Singh D. Interleukin 27 (IL-27) alleviates bone loss in estrogen-deficient conditions by induction of early growth response-2 gene. *Journal of Biological Chemistry*. 2017 Mar 17;292(11):4686-99.
  - 46) Robaszekiewicz A, Qu C, Wisnik E, Ploszaj T, Mirsaidi A, Kunze FA, Richards PJ, Cinelli P, Mbalaviele G, Hottiger MO. ARTD1 regulates





- osteoclastogenesis and bone homeostasis by dampening NF- $\kappa$ B-dependent transcription of IL-1 $\beta$ . Scientific reports. 2016 Feb 17;6(1):1-4.
- 47) Cheng R, Wu Z, Li M, Shao M, Hu T. Interleukin-1 $\beta$  is a potential therapeutic target for periodontitis: a narrative review. International journal of oral science. 2020 Jan 2;12(1):1-9.
- 48) Holen I, Lefley DV, Francis SE, Rennicks S, Bradbury S, Coleman RE, Ottewell P. IL-1 drives breast cancer growth and bone metastasis in vivo. Oncotarget. 2016 Nov 15;7(46):75571.
- 49) Amarasekara DS, Yun H, Kim S, Lee N, Kim H, Rho J. Regulation of osteoclast differentiation by cytokine networks. Immune network. 2018 Feb 1;18(1).
- 50) Liao LN, Li CI, Wu FY, Yang CW, Lin CH, Liu CS, Lin WY, Li TC, Lin CC. Important gene-gene interaction of TNF- $\alpha$  and VDR on osteoporosis in community-dwelling elders. Plos one. 2019 Dec 30;14(12):e0226973



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