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Opinion

Progranulin is Associated with Osteoporosis by Inhibiting Osteoclastogenesis and Promoting Osteoblastogenesis

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Opinion

Osteoporosis is a systemic metabolic bone disease characterized by bone loss and microstructural abnormality of bone tissue, which leads to the increase of risky of bone fractures [1]. For bone metabolism under physiological condition, osteoblasts and osteoclasts are maintained in an appropriate dynamic balance. However, the essential reason for the osteoporosis lies in the disturbance of this bone homeostasis, that is, excessive bone resorption which is mediated by osteoclast or inadequate bone formation mediated by osteoblast or both [2,3]. Recent studies indicated that osteoclast differentiation is mainly regulated by Macrophage Colony-Stimulating Factor (M-CSF) and Receptor Activator of Nuclear Factor KB Ligand (RANKL) [4]. Kobayashi, et al. found tumor necrosis factor α (TNFα) promoted osteoclast differentiation through the ODF/RANKL-RANK signaling. In addition, it's reported that TNFα inhibits osteoblastogenesis by suppressing the recruitment of osteoblast and inhibiting the expression of matrix protein gene via β-catenin pathway [5,6]. It's well-accepted that TNFα and its signaling pathways plays an important role in and might be a potential target for osteoporosis.

Progranulin (PGRN) is a growth factor with unique "beeds-on-string" structure which plays a critical role in various pathological and physiological processes, including inflammation, cell growth, wound healing and tumorigenesis [7-10]. Interestingly, PGRN was found to restrain its strong anti-inflammatory effect in many diseases [10-13]. Additionally, Tang et al revealed PGRN's effect by revealing its receptors. PGRN effectively binds to Tumor Necrosis Factor Receptors (TNFRs). There are two major receptors for TNFRs, namely TNFR1 and TNFR2. Basically, TNFR1 was well-studied and accepted as mediator of pro-inflammatory processes. On the other hand, TNFR2 was less understood. Based on previous studies, TNFR2 plays a protective role in heart failure, cartilage repair and so on. Importantly, for binding to TNFR1, PGRN shows comparable binding affinity with TNFα. However, for binding to TNFR2, PGRN demonstrated even much higher binding affinity than TNFα. Given the fact that PGRN and TNFα binds to the same receptor, many studies found PGRN exerts its effect by inhibiting TNFα-mediated signaling, including inflammatory arthritis and intervertebral disc degeneration.

Based on previous studies, recent studies demonstrated that PGRN plays critical roles in bone metabolism [14,15]. Tang et al found that overexpression of TNFα resulted in promotion of calvarial osteoclast differentiation and deletion of PGRN further enhanced this process by taking advantage of the mice models [14]. Besides the cell-based experiment, Noguchi et al used genetically-modified mice model confirmed that loss of PGRN lead to bone loss compared to their control littermates. They illustrated PGRN played a crucial role in bone metabolism by inhibiting TNFα-induced Osteoclastogenesis [16]. Furthermore, Zhao et al also found that Titanium particles can promote the formation of osteoclasts in the mouse calvaria osteolysis model via NF-KB signal pathway. However, PGRN can largely attenuate this effect to prevent osteolysis [17]. Moreover, PGRN inhibited osteoclastogenesis by down-regulating the phosphorylation of ERK1/2 and p38.

Importantly, besides PGRN's role in osteoclast differentiation, it's reported that PGRN also plays a role in promoting bone formation [15]. Zhao, et al. established several animal models, including surgically-induced bone defect, bone nonunion and ectopic bone formation mice models. By using these in vivo experiments, they found PGRN deficiency prolonged the bone healing and recombined PGRN accelerated bone healing process. Moreover, BMP-2, which is known to be a criterial role in bone regeneration [18,19], was required for PGRN to induce bone formation. In addition, PGRN's promotion effect in bone healing primarily depends on TNFR2 pathway. Interestingly, another study

demonstrated Erk1/2 pathway was a negative regular in matrix mineralization of osteogenic cells [20]. Collectively, PGRN acts as a critical molecule in bone metabolism by inhibiting TNF-α mediated destructive activities and promoting BMP-2 induced protective activities [15].

In conclusion, PGRN plays a role in osteoclastogenesis and osteoblastogenesis. Based on previous studies, we speculate there may be a potential association between PGRN and osteoporosis. However, whether serum levels of PGRN alters in the osteoporosis population and the role of PGRN in osteoporosis is still not clear. Additionally, whether PGRN exerts its effect in osteoporosis through TNFRs and the mechanism involved needs to be further discussed.

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