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The Expression of NFATc1 Is Influenced by Indoxyl Sulfate through Aryl Hydrocarbon Receptor to Effect Osteoclasts Proliferation and Differentiation

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Objectives: RANKL induces the expression of NFAT, cytoplasmic, calcineurin-dependent 1 (NFATc1), which is an important mediator of osteoclastogenesis to play an essential role in the up-regulation of expression in osteoclast precursors within the bone microenvironment. Additionally, AhR (Aryl Hydrocarbon Receptor) has a potent role in RANKL-mediated osteoclastogenesis, and osteoclast differentiation via the AhR signaling is also regulated in a RANKL/NFATc1 axis dependent manner. During the progression of CKD, indoxyl sulfate (IS), can influence osteoclast proliferation and differentiation. Therefore, our aim is to evaluate how IS induces the expression of NFATc1 via AHR pathway to impact the proliferation of pre-osteoclasts and the differentiation of osteoclasts.

Methods: We cultured osteoclasts from Raw 264.7 cells for observation on day 3 and day 6. We examined IS in various concentrations and measured activation of the AhR pathway in osteoclastogenesis related to the protein expression of AhR and NFATc1. We clarified the expression of osteoclastogenesis related NFATc1 signaling with IS culture in both cells. In addition, we used cell counting kit-8, tartrate-resistant acid phosphatase (TRAP) stain, Western blot, Real-time PCR, and confocal microscopy to assess pre-osteoclast proliferation and osteoclasts differentiation in different concentrations of IS.

Results: Our preliminary results showed that the concentrations of IS in 10, 20, 100 uM can increase the expression of AHR, NFATc1 and the proliferation of pre-osteoclast in day 3. Conversely, the expressions of AHR, NFATc1 are decreased, and under higher concentration of IS in 20, 100, 250 uM, there is a decrease in differentiation of osteoclasts on day 6.

Conclusions: This research provides that IS can increase the proliferation of pre-osteoclasts through AhR /NFATc1 signaling transiently. In opposition, IS suppress osteoclasts differentiation through AhR/NFATc1 signaling in long term situation. Thus, AhR/NFATc1 pathways may be novel targets for future treatments of uremic osteoporosis.