論 文 要 旨

Interleukin-1ß inhibits bone morphogenetic protein-9- induced osteoblastic differentiation of human periodontal ligament fibroblasts

（ヒト歯根膜線維芽細胞における
IL-1βのBMP-9誘導骨芽細胞様分化抑制作用について）

江部　由佳梨

Bone morphogenic protein-9 (BMP-9) has been shown to potently induce osteoblastic differentiation of periodontal ligament fibroblasts (PDLFs) and may be a candidate therapeutic agent for periodontal tissue healing/regeneration, but the effect of the inflammatory environment of periodontitis on such approaches is unclear. We investigated whether interleukin-1β (IL-1β) affected BMP-9-mediated osteoblastic differentiation of human (h) PDLFs. IL-1β suppressed BMP-9-induced osteogenic differentiation of hPDLFs, as evidenced by reduced alkaline phosphatase (ALP) activity and mineralization, and downregulated expression of BMP-9-mediated bone-related genes, *RUNX2*, *SP7*, *IBSP*, and *SPP1*. In hPDLFs with or without BMP-9, IL-1β increased the protein expression of activin A, a BMP-9 antagonist, and decreased follistatin protein, an antagonist of activin A. Similarly, IL-1β upregulated the expression of the activin A gene and downregulated that of the follistatin gene. Notably, follistatin re-established BMP-9-induced ALP activity suppressed by IL-1β. Activin A inhibited the expression of BMP-9-responsive genes and BMP-9-induced ALP activity, while follistatin re-established them. Finally, extracellular signal-regulated kinase 1/2 (ERK1/2), p38, and nuclear factor-kappa B (NF-κB) inhibition significantly blocked IL-1β-induced activin A gene expression. Our data indicate that IL-1β inhibits BMP-9-induced osteoblastic differentiation of hPDLFs, possibly by promoting activin A production via the ERK1/2, p38, and NF-κB pathways.