

## 論文審査の要旨

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**Intercellular Signaling between Ameloblastoma and Osteoblasts**

Ameloblastoma is an odontogenic tumor located in the bone jaw with clinical characteristics of extensive bone resorption. It is a locally invasive tumor with a high recurrence rate despite adequate surgical removal. In bone disease, tumors and other cells in the bone microenvironment contribute to the pathogenesis of tumor growth. However, the effect of osteoblasts on ameloblastoma cells is not well understood, and there has been limited research on interactions between them.

This study investigated interactions between ameloblastoma cells and osteoblasts using a human ameloblastoma cell line (AM-3 ameloblastoma cells) and a murine pre-osteoblast cell line (MC3T3-E1 cells). For cytokine production assay, MC3T3-E1 osteoblast cells were treated in the presence of D-KSFM (50%(v/v)), or AM-3 CM (50%(v/v)) in the presence or absence of IL-1Ra (100 ng/mL) for 24 or 72 h. For MMPs assay, AM-3 ameloblastoma cells were treated in the presence of  $\alpha$ -MEM/FBS (50%(v/v)) or MC3T3-E1 CM (50%(v/v)). The expressions of MMP-2 were also investigated using western blot analysis.

Treatment with AM-3-conditioned medium induced inflammatory cytokine production of IL-6, MCP-1, and RANTES by MC3T3-E1 cells. The use of an IL-1 receptor antagonist suppressed the production of these inflammatory cytokines by MC3T3-E1 cells stimulated with AM-3-conditioned medium. The MC3T3-E1-conditioned medium triggered the expression of MMP-2 by AM-3 cells. Furthermore, MC3T3-E1 conditioned media accelerated the proliferation and migration activity of AM-3 cells.

In conclusion, ameloblastoma cells stimulated osteoblast to produce IL-6, MCP-1, and RANTES, which can promote tumor growth and modify the bone remodeling process by inducing osteoclastogenesis. Osteoblast-derived factors induced the production of MMP-2 by ameloblastoma cells, which could degrade extracellular matrix of the bone. Furthermore, unidentified factors from osteoblast CM accelerated the proliferation and migration of AM-3 ameloblastoma cells. These intercellular signaling between ameloblastoma cells and osteoblasts may play multiple roles in the pathogenesis of ameloblastoma.

よって本研究は学位論文として十分な価値を有するものと判定した。