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Hypoxia enhances periodontal ligament stem cell proliferation via the MAPK signaling pathway

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ABSTRACT. There is high incidence of periodontal disease in high-altitude environments; hypoxia may influence the proliferation and clone-forming ability of periodontal ligament stem cells (PDLSCs). The MAPK signaling pathway is closely correlated with cell proliferation, differentiation, and apoptosis. Thus, we isolated and cultured PDLSCs under hypoxic conditions to clarify the impact of hypoxia on PDLSC proliferation and the underlying mechanism. PDLSCs were separated and purified by the limiting dilution method and identified by flow cytometry. PDLSCs were cultured under hypoxic or normoxic conditions to observe their cloning efficiency. PDLSC proliferation at different oxygen concentrations was evaluated by MTT

assay. Expression of p38/MAPK and MAPK/ERK signaling pathway members was detected by western blotting. Inhibitors for p38/MAPK or ERK were applied to PDLSCs to observe their impacts on clone formation and proliferation. Isolated PDLSCs exhibited typical stem cell morphological characteristics, strong abilities of globular clone formation and proliferation, and upregulated expression of mesenchymal stem cell markers. Stem cell marker expression was not statistically different between PDLSCs cultured under hypoxia and normoxia ($P > 0.05$). The clone number in the hypoxia group was significantly higher than that in the control ($P < 0.05$). PDLSC proliferation under hypoxia was higher than that of the control ($P < 0.001$). p38 and ERK1/2 phosphorylation in hypoxic PDLSCs was markedly enhanced compared to that in the control ($P < 0.05$). Either P38/MAPK inhibitor or ERK inhibitor treatment reduced clone formation and proliferation. Therefore, hypoxia enhanced PDLSC clone formation and proliferation by activating the p38/MAPK and ERK/MAPK signaling pathways.

Key words: Hypoxia; Periodontal ligament stem cells; Cell proliferation; Clone formation