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Paracrine- and Cell-Contact-Mediated Immunomodulatory Effects of Human Periodontal Ligament-Derived MSCs

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Objectives Human periodontal ligament-derived mesenchymal stromal cells (hPDL-MSCs) have a high therapeutic potential, largely dependent on their immunomodulatory properties. The mechanisms of this immunomodulatory activity are versatile and regulated by various inflammatory cytokines produced by the immune cells. In this study, we directly compare the contribution of various mechanisms on the reciprocal interaction of hPDL-MSCs and allogeneic $CD4^+$ T lymphocytes using different *in vitro* co-culture models at different inflammatory milieus.

Methods The reciprocal interaction between hPDL-MSCs and $CD4^+$ T lymphocytes was investigated in three different co-culture models: direct with or without insert and indirect with 0.4mm-pored insert. Co-culture was performed with untreated, interleukin (IL)-1b, or tumor necrosis factor (TNF)-a - treated hPDL-MSCs, and $CD4^+$ T lymphocyte proliferation was activated by phytohemagglutinin. In $CD4^+$ T lymphocytes, proliferation, viability, and cytokine secretion were investigated. The gene expression of soluble and membrane-bound immunomediators was investigated in the co-cultured hPDL-MSCs.

Results $CD4^+$ T lymphocyte proliferation and viability were inhibited by hPDL-MSCs. In untreated hPDL-MSCs, this effect was more pronounced in the direct co-culture model. Co-culture of $CD4^+$ T lymphocytes with hPDL-MSCs in the direct co-culture model without inserts resulted in a strikingly higher $CD4^+$ T lymphocyte cell death rate. Adding IL-1b to the co-culture models resulted in substantial $CD4^+$ T lymphocyte response alterations. In contrast, adding TNF-α had only moderate effects. The changes in $CD4^+$ T lymphocyte parameters upon adding IL-1β or TNF-α in a direct co-culture model without insertion were qualitatively different from those observed in two other models. The immunomediator gene expression in untreated and cytokine-triggered hPDL-MSCs also showed some variability depending on the model.

Conclusions The inflammatory environment affects both paracrine and cell-to-cell contact interaction between hPDL-MSCs and $CD4^+$ T lymphocytes. This fact should be considered by comparing the outcomes of the different models.