Effects of Cyclosporin A on TLR-Mediated Responses of Gingival Fibroblasts

Department of Periodontology, Nagasaki University Graduate School of Biomedical Sciences

Ana Maria Masae Suzuki, Atsutoshi Yoshimura, Takashi Kaneko, Yoshitaka Hara

Key Words: cyclosporin A, gingival fibroblast, TLR

Objective

Cyclosporin A (CsA) is an immunosuppressant prescribed to prevent rejection of organ transplantation and for the treatment of some autoimmune diseases. A common side effect of CsA is gingival overgrowth. The frequency and severity of CsA-induced gingival overgrowth is associated with oral hygiene status. Bacterial components in dental plaque induce gingival inflammation through the activation of Toll-like receptors (TLRs) and it may contribute to CsA-induced gingival overgrowth. The aim of this study is to assess the effects of CsA on the responses of human gingival fibroblasts (HGFs) to various TLR ligands.

Materials and methods

HGFs from four donors were stimulated with Pam3CSK4 (TLR2 ligand), lipid A (TLR4 ligand) and poly I:C (TLR3 ligand) in the presence or absence of CsA. Following 45 minutes incubation, the nuclear translocation of NF-κB in HGFs was measured by electrophoretic mobility shift assay. Following 18 hours incubation, CD54 (ICAM-1) expression was analyzed by flow cytometry and productions of IL-6 and IL-8 were measured by enzyme-linked immunosorbent assay. The proliferation of HGFs was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay.

Results

Each TLR ligand induced nuclear translocation of NF-κB, CD54 expression and productions of IL-6 and IL-8 in the HGFs with the intensities peculiar to each cell line. The proliferation rates of HGFs were diminished by each TLR ligand. CsA per se did not induce nuclear translocation of NF-κB, CD54 expression and productions of IL-6 and IL-8 in the HGFs, but it enhanced those responses induced by each TLR ligand in some HGF cell lines. The effect of CsA on the cell activities of HGFs varied among the cell line, but the proliferation rates diminished by each TLR ligand were augmented in the presence of CsA.

Conclusions

CsA synergistically worked with each TLR ligand in terms of the induction of NF-κB activation, CD54 expression and IL-6 and IL-8 productions in HGFs, but opposed to the inhibitory effect of TLR ligands on the proliferation rate. These effects of CsA on TLR-mediated responses of HGFs may contribute to the development of gingival overgrowth.