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Impaired resolution of inflammation and endotoxin tolerance induction in auto inflammation

Tigran K. Davtyan
Scientific Centre of Drug and Medical Technology Expertise, Republic of Armenia

Abstract

Purpose: The nature of heightened endotoxin sensitivity state observed in Familial Mediterranean fever (FMF) at present remains unknown. To assess the possibility that IL-10 plays a role in setting inflammatory threshold we studied the IL-10 production by monocytes and dendritic cells and endotoxin tolerance induction in FMF patients.

Methods: 46 attack free FMF patients included in this study. The production of IL-10 by NLR- or TLR-agonists stimulated monocytes and dendritic cells assayed either by conventional ELISA and flow cytometry. Versatility of monocytes studied by measuring the production of IL-10 and IL-1β after stimulation by pro- and anti-inflammatory agents, and after stimulation arrest or a further counter stimulation. Monocyte endotoxin tolerance and cross-tolerance induction assayed by measuring the production of IL-1β, IL-10, TNF-α and IFN-γ after pre-stimulation by NLR- or TLR-ligands and after re-stimulation with LPS.

Results: In FMF patients we observed down-regulation of circulating CD36+ peripheral blood lymphoid cells but not monocytes, constitutively producing IL-10. The production of IL-10 by TLR- and NLR-agonists stimulated monocytes and dendritic cells is declined in FMF patients. Monocytes isolated from FMF patients failed to switch from a pro-inflammatory activated state to anti-inflammatory phenotype and still produce IL-1β but not IL-10, which cause impaired endotoxin tolerance and cross-tolerance induction. The IL-10 production and endotoxin tolerance induction by monocytes and dendritic cells restored by NOD2- ligand MDP and colchicine treatment.

Conclusion: Reduced IL-10 production associated with impaired setting of feedback inhibition of inflammatory response and caused impaired resolution of inflammation and endotoxin tolerance induction.