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SOCS1 mediates IL-6 effects

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Keywords

IFN-?R, IL-6, SOCS1, Th1 differentiation

Context

Cytokines are the strongest regulators of T-cell differentiation. Interleukin (IL)-12 and interferon (IFN)-? drive Th1 differentiation whereas IL-4 promotes Th2 differentiation. It has been shown that IL-6 derived from antigen presenting cells initiates IL-4 production in naive $CD4^+$ T cells which in turn polarizes them to the Th2 phenotype. In this study the mechanisms by which IL-6 inhibits Th1 cell differentiation were evaluated.

Significant findings

A negative effect of IL-6 on Th1 differentiation of $CD4^+$ T cells was demonstrated in different *in vitro* systems and *in vivo*. IL-6 reduced the level of IFN-? production in the presence or absence of exogenous IL-12. The presence of anti-IL-4 antibody did not prevent the suppressive effect of IL-6. Interestingly, IL-6 did not influence IFN-? production by $CD4^+$ T cells from mice deficient in IFN-? receptor a (IFN-?Ra). A decrease in IFN-?-induced STAT-1 phosphorylation in the presence of IL-6 was observed, suggesting that IL-6 might modulate Th1 differentiation by interfering with IFN-?R signaling. Consequently, the effect of IL-6 on IFN-? production by T cells deficient in suppressor of cytokine signalling 1 (SOCS1) and by wild-type cells was determined. While IL-6 inhibited IFN-? production by wild-type cells stimulated with anti-CD3 and anti-CD28, it failed to downregulate the production of IFN-? in SOCS1-deficient $CD4^+$ T cells. Moreover, IL-6 inhibited STAT-1 phosphorylation in $CD4^+$ T cells from IFN-?$^{-/-}$SOCS1$^{+/+}$ mice, but did not alter STAT-1 phosphorylation in T cells from IFN-?$^{-/-}$ SOCS1$^{-/-}$ mice.

Comments

IL-6 is produced by a variety of cell types such as macrophages, fibroblasts, endothelial cells, and activated T and B cells. IL-6 prevents resting T cells from undergoing apoptosis and regulates T-cell survival. Moreover, the systemic administration of IL-6 suppressed the development and the progression of experimental autoimmune encephalomyelitis, presumably by limiting the generation of Th1 effectors. The data in this study demonstrate that the negative effect of IL-6 on Th1 differentiation was independent of IL-4. IL-6 affected IFN-? production and IFN-?R signaling. Previous studies have demonstrated that IL-6-induced gene expression of the suppressor protein SOCS1 results in negative regulation of cytokine signaling. Thus, increased levels of SOCS1 might inhibit signaling triggered by IFN-?/IFN-?R ligation. In this regard, STAT-1 phosphorylation was prevented in CD4+ T cells from IFN-?$^{-/-}$ SOCS1$^{+/+}$ transgenic mice. Together, the suppression of Th1 commitment by IL-6 is mediated by SOCS1 via interference with IFN-?R signaling, and the effect of IL-6 on Th2 differentiation results from the initiation of IL-4 production. Therefore, the result of the pleiotropic functions of IL-6 is the modulation of Th1 or Th2 differentiation by two completely independent mechanisms.

Methods

ELISA, RNase protection assay, electrophoretic mobility shift assay

Additional information

References

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