Abstract

The development and function of T helper (Th) cells and regulatory T cells (Tregs) are plastic processes that are regulated by cytokines. In our project we first analyzed the effect of different cytokines on the development of induced (i) Tregs. It has been demonstrated that iTregs arise from $CD4^{+}CD25^{-}$ T cells upon stimulation with alloantigen in the presence of transforming growth factor β (TGF-β). The development of these Tregs and their proliferation were inhibited by interleukin (IL)-4 and IL-12. The aquired results also demonstrated distinct responses of naturally occuring (n) Tregs and iTregs to the regulatory action of IL-4 and an opposite role of IL-4 in maintenance of nTregs and iTregs phenotype.

An important role in the induction of T cell subsets may play also mesenchymal stem cells (MSCs) which can, under specific conditions, produce TGF-β and IL-6. Depending on the current production of TGF-β or IL-6, MSCs can qualitatively regulate the ration between Tregs and Th17 cells. Anti-inflammatory Tregs and pro-inflammatory Th17 cells are induced upon stimulation in the presence of TGF-β and TGF-β and IL-6, respectively. In addition to our previous work we studied the role of IL-12 in the development of Tregs and Th17 cells. It was shown that Treg and also Th17 cell differentiation was prevented by IL-12 as was the induction of Foxp3 transcription factor expression by TGF-β or RORγt transcription factor expression by TGF-β and IL-6. Moreover, IL-12 was able to alter the development of iTregs and Th17 cells even when added to the differentiating cells after 48 h of the culture. The cells activated in the presence of TGF-β and IL-12 had an increased expression of the Th1 transcription factor T-bet, produced Th1 cytokines interferon γ and IL-2 and expressed the phenotypic markers IL-18 receptor and C-C chemokine receptor type 5 which are characteristic for Th1 cells.

In conclusion, our findings contributed to the field of developmental plasticity of Tregs and Th cells and demonstrated the significant role of cytokines in this process. The results can also contribute to the improvement of therapeutic procedures where Tregs are used to treat severe autoimmune diseases or transplantation.