Abstract

Regulation of immune reactions represents an entire system of maintenance of homeostasis, self-tolerance, and host defense. Regardless of intensive research, the cellular and molecular insights into immunomodulation remain incomplete. Therefore, we aimed to study different approaches to modulate the immune system, primarily focused on the induction, expansion, and activation of immunoregulatory cells.

We analyzed the therapeutic effect of the combined action of mesenchymal stem/stromal cells (MSCs) and immunosuppressive drugs on the balance among T cell populations. We found that MSCs ameliorated unfavorable effects of immunosuppressants on T cell activation. As a result of this approach, T cell development was altered from the T helper (Th) 1, Th2, and Th17 cell polarization to anti-inflammatory regulatory T cell-mediated response. Additionally, we studied the effect of the immunoregulatory action of MSCs on B cells. We evaluated the impact of cytokine-primed MSCs on the induction of interleukin (IL)-10-producing B cells. Results revealed that interferon (IFN)-γ- and IL-4-primed MSCs suppressed the production of IL-10 by activated B cells. This suppression was dependent on cell-to-cell contact. In the case of IFN-γ-primed MSCs, the inhibition of IL-10 secretion involved the cyclooxygenase-2 signaling pathway, but the suppression mediated by IL-4-primed MSCs was independent of this enzyme and its products.

Further, we investigated the role of the cytokine milieu in the development of IL-10-producing B and T cells. Moreover, we analyzed the involvement of GATA-3 and FoxP3 transcription factors in IL-10 production by activated B cells. IFN-γ significantly enhanced the proportion of IL-10-producing B cells, but IL-4 and transforming growth factor (TGF)-β decreased the percentage of these cells. The IL-10 expression in stimulated B cells was independent of GATA-3 and FoxP3 expression, contrasting with findings in T cells, where IL-10 expression was associated with GATA-3 or FoxP3 transcription factor after IL-4 or TGF-β stimulation. Simultaneously, we found that stimulated B cells, in comparison to stimulated T cells, nonspecifically bound R-phycoerythrin-conjugated antibodies during intracellular marker staining. Thus, the data acquired using these antibodies for intracellular staining of activated B cells must be taken with precaution.

The results presented in this thesis highlight the importance of regulation of immune response and its targeted modulation that can provide advanced therapeutic strategies for the treatment of autoimmune diseases or achievement of transplantation tolerance. Furthermore, the data stress the pivotal role of the cross-talk between cells and the local environment in the induction, expansion, and activation of immunoregulatory cells.