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Editorial

Interleukin 7, maestro of the immune system

Pivotal initial studies on the cloning of IL-7 in 1988 [1] and IL-7Rα two year later [2] ushered in a flurry of activity on the physiological function of IL-7. The severe lymphopenia seen in IL-7$^{-/-}$ and IL-7Rα$^{-/-}$ mice [3,4] and also in a subset of SCID patients [5] established that contact with IL-7 is crucial for development and maintenance of the immune system, not only for T and B cells but also for certain components of the innate immune system. Indeed, in terms of its pervasive influence on a wide variety of cells types, IL-7 has emerged as the master controller of both the adaptive and innate immune systems. In this volume a number of noted authorities provide a comprehensive overview of IL-7 physiology and function, detailing the synthesis and cell sources of this cytokine, the various cell types under IL-7 control and the consequences of IL-7 deficiency or defective IL-7 signalling in both health and disease.

IL-7 is a member of the γc family of cytokines and binds to a cell-surface receptor composed of IL-7Rα (CD127) and the common γ-chain (CD132) [6,7]. As discussed by Huang and Luther, the IL-7R is expressed mainly by lymphocytes, notably T cells, NK cells, and subsets of B cells, but is also found on various components of the innate immune system such as macrophages, dendritic cell subsets and lymphoid tissue inducer cells (LTi); in addition, IL-7R is expressed on certain non-haemopoietic cells such as blood endothelial cells. While the two-chain IL-7R binds solely to IL-7, IL-7Rα can form a heterodimer with another chain, thymic stromal lymphopoietin (TSLP) receptor, thus allowing binding of a related cytokine, TSLP. For IL-7, signalling recruits Jak1 and Jak3 which leads to dimerization and translocation of STAT5 to the nucleus and gene transcription; activation of the PI3 kinase pathway and upregulation of Bcl-2 then promotes cell proliferation and survival. With regard to synthesis, IL-7 is secreted largely by specialized stromal cells and vascular endothelium in sites of lymphopoiesis and is presented on the extracellular matrix bound to heparin sulphate proteoglycans.

The paucity of lymphocytes in IL-7$^{-/-}$ and IL-7R$^{-/-}$ mice is especially striking for T cells. As summarized in the chapters by Hong et al. and Ceredig and Rolink, IL-7 deficiency results in a marked decline in the cellularity of the thymus due to a block in development of CD4^{-}8^{-} "double-negative" (DN) cells, specifically at the DN3 stage which correlates with initial expression of IL-7R on maturing thymocytes. At this stage, IL-7 plays a vital role in driving cell proliferation. In normal mice, IL-7R expression is downregulated at the DN4 and "double-positive" (DP) CD4^{+}8^{+} cell stages in parallel with upregulation of the αβ TCR receptor, thereby depriving DP cells of stimulation via IL-7 and paving the way for thymocyte selection via TCR/MHC contact. The small component of MHC-selected mature thymocytes arising from DP cells regains sensitivity to IL-7 through re-expression of IL-7R. High IL-7R expression is maintained on post-thymic naïve CD4 and CD8 T cells, but is lost during the immune response, then re-expressed at the level of resting memory cells.

Maintenance of IL-7R expression on naïve and memory T cells plays a vital role in controlling normal T cell homeostasis. As outlined in the chapter by Carrette et al., sensitivity to IL-7 is important for keeping mature T cells alive in interphase, largely by inducing expression of Bcl-2. Signaling pathways controlling sensitivity to IL-7 and molecular mechanisms regulating IL-7R expression are beginning to be defined in more depth. Sensitivity to IL-7 is dependent on continuous contact with self-MHC ligands and is dysregulated in conditions of lymphopenia, e.g. when mature naïve T cells are transferred to lymphopenic hosts. In this situation, lack of competition causes levels of IL-7 to rise, thereby increasing the intensity of IL-7 signalling and driving the responsive T cells to proliferate. Such lymphopenia-induced "homeostatic" proliferation (LIP) causes the cells to expand in number and switch to memory cells. LIP also applies to human T cells and leads to expansion of residual mature T cells after bone marrow transplantation.

As for T cells, IL-7$^{-/-}$ and IL-7R$^{-/-}$ mice show a marked decrease in numbers of B cells. As discussed in two separate chapters by Ceredig and Rolink, and Corfe and Paige, IL-7R is upregulated on Pre-pro B cells and their immediate progeny, Pro-B and Pre-B2 cells. During these stages, contact with IL-7 augments the expansion of early B cells and also prevents differentiation of these cells. Thereafter, IL-7R expression is downregulated at the late Pre-B2 stage and remains low or absent on immature IgM^{+} B cells and also on typical mature B cells. Unlike T cells, the survival of mature B cells is IL-7 independent, these cells being kept alive through contact with other cytokines, notably BAFF/BLyS. For initial B cell formation, it should be noted that, although IL-7 is crucial for the generation of typical B cells in adult bone marrow, the initial formation of B cells in fetal liver is largely IL-7 independent, perhaps reflecting a compensatory role for TSLP during this stage. Interestingly, some B cell subsets in adults, namely B1 B cells and marginal zone B cells, seem to be largely IL-7 independent, which is thought to reflect that most of these cells are the descendants of cells arising in the fetal liver. It is important to emphasize that the evidence on the role of IL-7 on the initial formation of B cells relies heavily on studies with mice. The situation in humans is quite different. Thus, studies on SCID patients indicate that deficiency of IL-7 signalling in humans impairs the formation only of T cells and not B cells. The reason for this difference between mice and humans is still unclear.

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The wide distribution of IL-7R expression on many cell types has focussed attention on the role of IL-7 on non-lymphoid cells, especially LTi cells and also natural helper cells (nuocytes). As discussed in the chapters of Huang and Luther, Kang and Coles, and Vonarbourg and Diefenbach, IL-7 is required for promoting the survival of LTi cells, which control the development of lymph nodes, and also Peyer's patches and lymphoid clusters (cryptopatches) in the small intestine. LTi cells express the transcription factor RORγt and synthesize IL-17 and IL-22; IL-7 functions by stabilizing RORγt and upregulating expression of lymphotoxin LTα1β2, a ligand for LTβR, thereby inducing expansion and tissue recruitment of LTi. However, precisely how LTi cells control the formation of tertiary lymphoid organs is poorly understood and is the topic of intensive investigation.

Documentation of the many functions of IL-7 in mice has spurred interest in the role of IL-7 in human disease. This topic is addressed in the articles of Mazzucchelli et al. and Lundstrom et al. As mentioned earlier, defects in IL-7 signalling account for certain forms of human SCID. In addition, polymorphisms of IL-7R are associated with a number of autoimmune diseases, including multiple sclerosis. Why IL-7R polymorphisms predispose to autoimmune disease is unclear but gain-of-function mutations leading to an increase in IL-7 signalling is a likely possibility. Such mutations can also be associated with acute lymphoblastic leukemia. As discussed in the chapter of Crawley and Angel, alterations in IL-7 signalling occur in HIV and other chronic viral infections as well as in cancer. In these diseases, IL-7R expression is reduced and correlates with immunodeficiency.

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