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IL-17 production by thymocytes upon CD3 stimulation and costimulation with microbial factors

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Abstract

IL-17 is a potent proinflammatory cytokine produced by activated memory T cells. Recent studies in both human autoimmune diseases and in their animal models have indicated that IL-17 rather than IFN-γ might be the essential T-cell effector cytokine in the T-cell mediated autoimmune process. Since the thymus has a central role in maintaining T-cell self-tolerance and disturbance of thymic self-tolerance is implied in various autoimmune diseases, we here investigated the capability of murine thymocytes to produce IL-17. Our results indicate that thymocytes are a potent source of IL-17 in response to CD3 stimulation and various microbial immune stimuli and thereby show different patterns in the expression of the proinflammatory cytokines IFN-γ and IL-17. In addition, strong differences between thymocytes and splenocytes were detected. Altered IL-17 production by thymocytes upon contact with foreign pathogens might be a key regulator in the education of adaptive immunity.
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1. Introduction

The thymus is considered as major organ for the maintenance of central tolerance shaping the T-cell receptor (TCR) repertoire by positive and negative selection and therefore largely avoiding the appearance of autoreactive T cells [1,2]. Cytokines and chemokines are implied to have an essential role in this process [3–5], since the cytokine environment which CD4 and CD8 effector cells encounter during their education in the thymus and during engagement of the TCR is a key factor determining the quality of the response of these cells. CD4 cells in general have been traditionally classified into Type-1 (Th1) and Type-2 (Th2) cells. Type-1 (Th1) polarized T cells, produce high amounts of IFN-γ and have been demonstrated to exert a central role in T-cell-mediated autoimmune disease [6,7]. Recently, interleukin 17 (IL-17) which also is a potent pro-inflammatory cytokine produced by activated T cells was shown to be the key cytokine produced by a new line of T helper cells (Th17) [8,9]. Its effects and the emerging associations with major human autoimmune diseases and their corresponding animal models suggest that IL-17 may have a significant regulatory role in inflammatory processes in general [10,11]. Overproduction of IL-17 has been associated with several chronic inflammatory disease conditions, including autoimmune diseases, suggesting a central role in T-cell-mediated inflammation in these diseases [12–17]. IL-17-expressing T cells seem to require APCs that show IL-23 expression to be activated [18]. Recent studies have suggested that the IL-23/IL-17 axis is an important inflammatory cytokine pathway operating autoimmune disease and that the IL-12/IFN-γ pathway is not necessarily required [19–22]. On the other hand, IL-17 has been shown to exert a pivotal protective role in host defence against infectious agents, in particular bacterial agents

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[11]. Therefore, mechanisms which lead to the generation of IL-17-producing T cells and factors which steer T-cell IL-17-production are currently of major interest in several fields of T-cell immunology.

It has been shown that the developing T cell in the thymus and the local milieu in which it is educated can be influenced by a spectrum of different microbial factors [23–28]. Several of these have been implied in the pathogenesis of autoimmune diseases, but also in stimulating protective immunity against infections and tumors. The mechanism via which many of these microbial substances have been shown to exert their function is via ligation of toll-like receptors (TLR) on the cell surface of immune cells. Immunological tools to paradigmatically study immune stimulation by microorganisms include various pathogen-associated molecular patterns like CpG oligonucleotides or double-stranded RNA (poly I:C), as well as secreted microbial toxins like pertussis toxin (PTX) or cholera toxin (CTX). All these microbial stimuli have been shown to trigger T-cell mediated autoimmune disease in animal models [29–32]. Previous studies have investigated the capability of mature T cells to produce

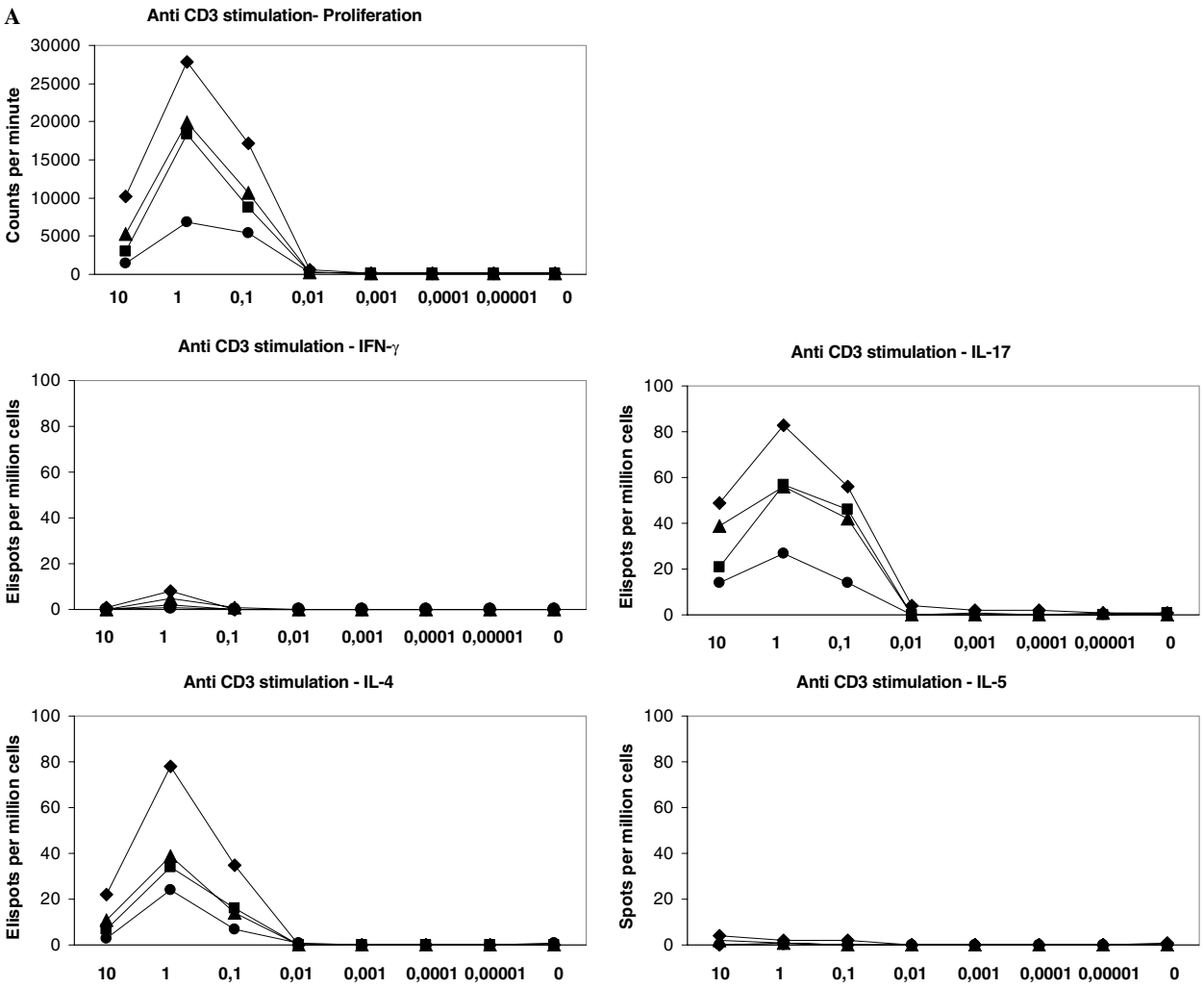

Fig. 1. (A) Proliferation and cytokine response of naïve thymocytes in response to CD3 stimulation as assessed by H3-thymidine incorporation assay and ELISPOT assays for the cytokines indicated. Thymocytes of eight individual naïve C57.BL/6 mice were freshly isolated ex vivo and cells pooled from two animals each were stimulated with an anti-CD3 antibody titrated from 10 to 0.00001 μg/ml as indicated. One of two experiments with similar results is shown. Each symbol reflects one pooled sample tested individually, with the same respective symbol used in all panels. (B) Proliferation and cytokine response of naïve thymocytes in response to LPS as assessed by H3-thymidine proliferation assay and ELISPOT assays for the cytokines indicated. Thymocytes of eight individual naïve C57.BL/6 mice were freshly isolated ex vivo and cells pooled from two animals each were stimulated with LPS titrated from 100 to 0.001 μg/ml as indicated. One of two experiments with similar results is shown. Each symbol reflects one pooled sample tested individually, with the same respective symbol used in all panels. (C) Intracellular FACS analysis of unstimulated thymocytes (upper row) compared to thymocytes stimulated with anti-CD3 (lower row). Cell populations were gated on $CD4^+$ single positive cells (left), $CD8^+$ single positive cells (second left), $CD4^+CD8^+$ double positive cells (second right) and $CD4^-CD8^-$ double negative cells (right). Cells positive for IL-17 are depicted in a histogram and the percentage of IL-17 positive cells is indicated. One out of three experiments with similar results is shown. (D) Cytokine production of thymocytes after CD3 stimulation in Balb/C and C57.BL/6 mice. Thymocytes of naïve female mice were freshly isolated ex vivo and stimulated with anti-CD3 antibody at 1 μg/ml. Each symbol represents an animal tested individually. Bars represent the mean. One of two experiments with similar results is shown.

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