Symposium E

Cytokines and immunity

SE-1

TRANSCRIPTIONAL REGULATION OF THE IL-23/IL-17 IMMUNE PATHWAY

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T_H17 is a novel T cell subset driven by TGF-β, IL-6 and IL-23. While TGF-β and IL-6 are sufficient for differentiation of naïve T cells into IL-17 producing cells, IL-23 is required for their expansion, survival and pro-inflammatory function. The hypothesis that T_H17 is a distinct T cell lineage predicts that TGF-β and/or IL-6 must promote the expression of a transcription regulator that controls the immune repertoire of the IL-23/IL-17 immune axis. Using Affymetrix gene-expression analysis, we found a number of T_H17 cell-specific novel genes encoding putative proteins with potential DNA binding activities. Genetic depletion experiments confirmed that one of these DNA binding proteins, orphan nuclear receptor-γt, is necessary for differentiation and function of T_H17 cells. Ectopic expression of this transcription factor is sufficient to induce IL-17A and IL-17F production. The identification of this transcription regulator provided further evidence that T_H17 is a distinct T cell lineage that has unique roles in immunity. The implications of these findings for IL-23/IL-17 immune axis regulation of organ-specific autoimmunity will be discussed.

SE-2

REGULATION OF IMMUNITY BY EPIDERMAL CYTOKINES

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The skin is an organ where interaction with the environment frequently induces immune responses. Immune responses can be regulated by keratinocytes, which are virtually “cytokine factories” since keratinocytes can produce a large number of soluble factors. These factors can act locally on neighboring immunocompetent cells, such as Langerhans cells, or systemically after gaining access to the circulation. Depending on the environmentally (e.g. ultraviolet radiation or infections) induced cytokine patterns immune responses are activated or quelled. An important cytokine for the induction of immunity is IL-15. Since the production of endogenous IL-15 is tightly regulated, IL-15 transgenic (tg) were generated, which overexpress the transgene in basal keratinocytes under control of the keratin 14 promotor. Utilizing IL-15 tg mice it was shown that IL-15 activated Langerhans cells were able to induce contact hypersensitivity responses to epicutaneously applied even suboptimal hapten concentrations. In addition, IL-15 tg mice showed enhanced anti-viral immunity since tg mice developed significantly smaller cutaneous HSV lesions compared to littermate controls. Cutaneous IL-15 expression induced also long lasting protective anti-viral immunity as evidenced by re-infection experiments with HSV, which could be transferred by injecting anti-HSV serum from HSV infected IL-15 tg mice into controls. These findings indicate that IL-15 induces protective anti-viral immunity possibly by connecting innate and adaptive immune responses. In further investigations the role of cutaneous IL-15 overexpression in tumor immunity has been analyzed in detail. These finding will be also presented and discussed during my presentation.

SE-3

THE ROLE OF IL-27 IN THE REGULATION OF INFLAMMATORY AUTOIMMUNE DISEASES

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IL-27 is a recently defined family member of the long-chain four-helix bundle cytokines, which consists of EBI3, an IL-12p40-related protein, and p28, an IL-12p35-related polypeptide. We have previously shown that during experimental autoimmune encephalomyelitis (EAE) and adjuvant induced arthritis (AA) the immune system selectively mount a beneficial anti self autoantibody response to a selected number of cytokines and chemokines that could be amplified by targeted DNA vaccines. This provided us a powerful tool to investigate the role of various mediators in the regulation of inflammatory autoimmune diseases. Here we show that during AA the immune system mounts a selective autoantibody response against the p28 subunit of IL-27 and that targeted DNA vaccines encoding this unit amplify this response in a beneficial manner. Purified antibodies could then transfer disease suppression. These antibodies could also suppress ongoing EAE in C57BL/6 mice. We have then used the well-defined EAE model to explore the mechanistic basis of IL-27 function in inflammatory of autoimmune diseases. Our results show that this cytokine further promotes the proliferation, cytokine production and inflammatory functions of antigen specific T cells during their activation, and by so doing promotes the dynamics of each disease. This may suggest anti IL-27 based therapy for T cell mediated autoimmunity.