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Interleukin 17: An Example for Gene Therapy as a Tool to Study Cytokine Mediated Regulation of Hematopoiesis

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Abstract Interleukin 17 (IL-17) is an essential proinflammatory T-cell derived cytokine with various biological actions. IL-17 was found to have a pivotal role in microbial host defense by interconnecting lymphoid and myeloid host defense. It also acts as a stimulatory hematopoietic cytokine by expanding myeloid progenitors and initiating proliferation of mature neutrophils. This article summarizes results to date on IL-17 research and discusses gene therapy based strategies that were employed to determine its biological functions and significance. A comprehensive working model for IL-17 is introduced. J. Cell. Biochem. Suppl. 38: 88–95, 2002. © 2002 Wiley-Liss, Inc.

Key words: interleukin 17 (IL-17); gene therapy; hematopoiesis; T-cells; cytokines

Interleukin 17 is a T-cell derived proinflammatory cytokine expressed by activated memory cells. It was initially described and cloned by Rouvier et al. and named CTLA8 [Rouvier et al., 1993]. It showed 58% homology to the T-lymphotropic herpesvirus samirii and had no resemblance to any other known cytokine or structural domain [Yao et al., 1995a,b]. Recently, lipoproteins were found to be specific stimuli for its expression [Infante-Duarte et al., 2000]. It appears that IL-17 expressing T-cells cannot be classified by the TH1/TH2 profile, as IL-17 expressing T-cells are characterized by co-expression of TNFα and GM-CSF [Mosmann et al., 1986; Infante-Duarte et al., 2000]. The corresponding receptor, IL-17R, was also found to be unique and without similarity to any other known protein or domain. Therefore, the IL-17 cytokine receptor system is considered a new and distinct signaling system. IL-17 is highly preserved between species with a 75% homology between human and mouse and murine IL-17 eliciting identical biological activity as its human counterpart on human cells. This high degree of preservation throughout species evolution indicates biological importance. Based on homology, subsequent studies have identified at least five other members of IL-17 related cytokines, named IL-17B through IL-17-F (IL-17B-F) [Li et al., 2000; Shi et al., 2000; Hymowitz et al., 2001; Lee et al., 2001].

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In Vitro Studies on IL-17

Although IL-17 expression is believed to be restricted to activated memory T-cells, the expression of the IL-17 receptor appears to be ubiquitous in most tissues. IL-17 receptors are highly expressed on fibroblasts and stroma cells [Rouvier et al., 1993; Yao et al., 1995a; Fossiez et al., 1996], and these cells are believed to be the predominant target cells for IL-17. The biological effects of IL-17 on fibroblasts or stroma cells in vitro are to release secondary cytokines and chemokines, specifically IL-1β, IL-6, IL-8, SCF, and cell adhesion molecules. Production of other proinflammatory substances such as prostaglandines and leukotrienes are also induced [Fossiez et al., 1996; Shalom-Barak et al., 1998; Kotake et al., 1999]. In vitro, IL-17 is able to maintain CD34 + selected stem cell derived human hematopoiesis in the presence of a stroma cell feeder layer, but not without the feeder layer [Fossiez et al., 1996]. This indicates that IL-17 action on primitive precursor cells can be achieved only via secondary cytokines released from the feederlayer.

The exact signaling cascades induced by IL-17 are not fully elucidated. However, signaling pathways may vary in different cell types and tissues. NFκB was found to be a central molecule within the IL-17 signaling pathways in different cells, such as chondrocytes, intestinal, and renal cells [Yao et al., 1995a; Fossiez et al., 1996; Shalom-Barak et al., 1998; Martel-Pelletier et al., 1999; Schwandner et al., 2000; Andoh et al., 2001]. NFκB activation is mediated via IκB kinases α and β, but this does not appear to be the exclusive mechanism. All three mitogen activated protein kinases (MAPKs) can be activated via IL-17 receptor signaling (extracellular signal regulated kinases ERK1 and ERK2, Jun NH2-terminal kinases (JNK), and p38 [English et al., 1999; Chang and Karin, 2001]. In macrophages, IL-17 could upregulate intracellular calcium concentrations [Jovanovic et al., 1998]. In some hematopoietic cell lines, IL-17 was found to signal via the JAK and STAT pathways [Subramaniam et al., 1999]. Therefore, IL-17 may exert effects on hematopoietic cells directly and not only via the induction of secondary cytokines.

IL-17 and its Role In Vivo

To determine in vivo biological functions of novel cytokines, transgenic and knockout mice have become established as standard models of biological research. However, potential drawbacks here are potential effects of the overexpressed or knocked out molecules during development and also compensatory mechanisms that might evolve during development. Either one could profoundly alter study endpoints and research outcomes. One example for knockout induced deranged organ development is the TNFα knockout mouse. TNFα is a critical host defense cytokine. However, TNFα knockout mice have a severely underdeveloped lymphatic system and lack entirely Peyer's patches [Neumann et al., 1996; Marino et al., 1997]. Therefore, any immunological research utilizing these animals will be confounded by these developmental abnormalities. For these reasons, it would be desirable to conduct studies on cytokines and chemokines in developmentally normal animals. Our group has attempted to engineer a transgenic mIL-17 mouse. However, all attempts were not successful, as we found this phenotype to be lethal early during development. An alternative strategy to engineer developmentally less compromised transgenic or knockout animals is through conditional transgene expression. However, most approaches do not completely silence transgene expression during early development and further refining of the technology is needed [Deng and Brodie, 2001; Meuwissen et al., 2001].

Although in vivo effects of novel cytokines and chemokines could be studied by administration of recombinant protein, pharmacological studies for the in vivo bio-availability are needed, and usually are not available. Additional protein modifications may be necessary in order to have a compound with in vivo activity [Bodine et al., 1993; Molineux et al., 1994].

Another alternative to study transient cytokine overexpression has been developed and pursued by our group is using adenovirus technology. Recombinant adenovirus is an efficient means of overexpressing proteins of up to 3,000 aminoacids (9,000 base pairs) at high levels over a period of several weeks in normal animals. This technology is readily available and can be employed in adult rodents and is also not limited by any strain or introduced genetic abnormalities. When adenovirus is injected intravenously, the majority of vector localizes to the liver where the transgene is expressed. This technique was first described in studies to determine the in vivo functions of TNFα, where an adenovirus engineered to encode a soluble TNFα receptor effectively blocked in vivo functions of TNFα [Kolls et al., 1994]. We have utilized this technology to transiently overexpress mIL-17 in normal C57*Bl6* mice. We also have engineered an adenovirus encoding the soluble mIL-17 receptor to generate a transient knockout in developmentally normal animals (AdmIL-17RFc) [Forlow et al., 2001; Ye et al., 2001a,b]. The soluble receptor functions by competing with the cell surface receptors for its binding with the soluble ligand as siphon, thus neutralizing its biological function. To enhance plasma half-life, the soluble receptor had been conjugated to murine IgG1-Fc. This system has potential advantages over antibody based in vivo cytokine neutralization, since with this technology small molecules can be encoded that have potentially enhanced pharmacokinetics with distribution to all tissues compared to the limited distribution of larger antibody molecules. Moreover, one single intravenous vector administration is sufficient to neutralize cytokines effectively over several weeks. In contrast, antibody based approaches

require repeated administration to the animal. One potential drawback of the adenovirus-mediated approach might be the release of adenovirus induced proinflammatory cytokines [Benihoud et al., 2000]. Therefore, experimental groups require two parallel control groups, one group is treated with an adenovirus encoding a non-relevant and ineffective transgene (e.g., luciferase) and another group should consist of saline (sham) treated animals. Given the complexity of in vivo cytokine cascades, the most accurate determination for in vivo function of individual cytokines would come from validating findings independently through different models and methods.

Thus, in vitro data are insufficient to make any in vivo predictions for cytokine or chemokine actions. Our initial in vivo studies using mIL-17 encoding adenovirus (AdmIL-17) showed splenomegaly and neutrophilia. More detailed investigation of hematopoiesis after mIL-17 expression demonstrated stimulation of hematopoiesis, specifically of granulopoiesis with the expansion of committed and immature progenitors in both spleen and bone marrow [Schwarzenberger et al.]. These data suggested that in vivo not only committed hematopoietic progenitors had been stimulated, but also hematopoietic stem cells. Based on the in vitro evidence, our model suggested these effects result from mIL-17 induced secondary cytokines that acted directly on hematopoietic stem cells. We found G-CSF to be secreted at high levels after mIL-17 expression, one of the most potent stimulators of granulopoiesis. A potent synergizer of G-CSF is stem cell factor (SCF) [Molineaux et al., 1991]. We also found that IL-17 induces expression of the membrane-associated form of SCF on bone marrow stroma cells. Studies conducted in SCF mutated mice proved that a significant portion of IL-17 mediated stimulation of granulopoiesis stems from induction of both SCF and G-CSF [Schwarzenberger et al.]. IL-17 also mobilized primitive repopulating stem cells in vivo, similar to mice treated with the combination of SCF and G-CSF [Molineaux et al., 1991; Briddell et al., 1993; Schwarzenberger et al.]. Current work in our laboratory continues to investigate other cytokines that might contribute to this action.

A mIL-17 receptor knockout mouse was generated by Dr. Jaques Peschon at Immunex. These mice, despite their housing in specific pathogen-free facilities, develop several months into their life focal alopecia, which progresses to skin ulcerations. This ulcerative syndrome involves mucous membranes of the mouth and eyes, resulting in inability of food intake and blindness. The syndrome is lethal within several weeks of its onset. The ulcers are colonized by staphylococcus species. Based on these observations, we concluded that these animals must have a deficiency in bacterial host defense. Given the profound stimulation of granulopoiesis caused by mIL-17, we suspected that lack of IL-17 would result in a defect involving neutrophils.

Experiments were conducted in a model of Klebsiella pneumonia in mice. We found that intranasally applied Klebsiella pneumonia was lethal at three-logfold less in IL-17R−/− mice compared to their littermate controls. Death occurred rapidly within several days of bacterial inoculation. IL-17R−/− had a significant delayed neutrophil influx into the lung compared to normal controls [Ye et al., 2001a,b]. The same results were also seen in normal C57*Bl/6* mice, which had been pretreated with adenovirus encoding the soluble IL-17 receptor (AdmIL-17RFc), thus neutralizing endogenous mIL-17. This second series of experiments independently validated the IL-17R−/− phenotype (Figs. 1 and 2) [Ye et al., 2001a,b]. In contrast to control animals, lungs in animals void of IL-17 or its receptor after bacterial inoculation showed severe necrosis of lung tissue and lack of neutrophil recruitment into the area of infection. These animals also failed in secretion of

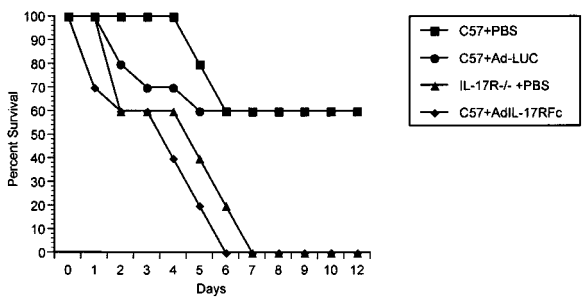

Fig. 1. Reduced survival in mice deficient of IL-17 signaling. Four groups of mice were intranasally inoculated with *Klebsiella pneumonia* (3×10^3 cfu/mouse) (n = 10/group): IL-17 receptor knockout mice (IL-17R-/-) and their sex and age matched littermate controls (C57*bl6*), IL-17 was neutralized in normal C57*Bl6* mice animals using an adenovirus expression construct encoding the soluble IL-17 receptor (AdIL-17RFc) and C57*Bl6* mice treated with control adenovirus (Ad-LUC). Survival is plotted against time.

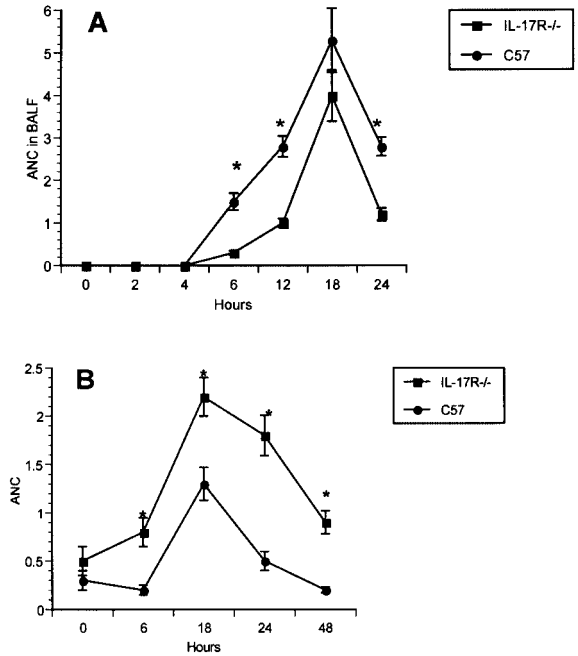

Fig. 2. Reduced and delayed neutrophil recruitment after pulmonary infection in IL-17R-/- mice. Absolute neutrophil count ($\times 10^5$/μl) from bronchoalveolar lavage fluid after intra nasal inoculation with 1×10^4 cfu of *Klebsiella pneumoniae*. IL-17R-/- mice and sex and age matched strain control C57*Bl6* mice were used (n = 5–8 per data point) (figure 2A). The absolute neutrophil counts obtained from peripheral blood in the same cohorts of mice are depicted in figure 2B. Asterisks indicate statistical significance of $P < 0.05$.

local neutrophil activating cytokines and chemokines, specifically of G-CSF and MIP-2 and SCF. We concluded that IL-17 is a critical cytokine that interconnects local myeloid host defense and lymphoid host defense. T-cells have been suspected to be regulators of hematopoiesis, although no mechanisms were found to explain this role. Our data suggest that IL-17 is a stimulatory cytokine linking localized inflammation to the production of neutrophils in hematopoietic organs, which is supported by the finding that IL-17 can mobilize and demarginate mature neutrophils, myeloid progenitors, and hematopoietic stem cells from hematopoietic organs [Schwarzenberger et al.].

The mobilization mechanisms for neutrophils and other hematopoietic cells are unknown, however, it is speculated that mobilizing compounds alter adhesion of hematopoietic cells within their microenvironment. Adhesion molecules are critical in regulating homing of hematopoietic cells. IL-17 was found to alter the adhesion molecule expression of ICAM 1 on fibroblasts. Mice lacking P-selectin, LFA-1, ICAM-1, Core-2-glucosaminyltransferase, P- and L-selectin, P-selectin and ICAM-1, L-selectin, and ICAM-1 have peripheral neutrophilia [Mayadas et al., 1993; Sligh et al., 1993; Bullard et al., 1995; Ellies et al., 1998; Steeber et al., 1998; Ding et al., 1999; Robinson et al., 1999]. Our collaborators found that G-CSF and mIL-17 were elevated proportionally to the degree of neutrophilia in CD18−/−, CD18−/− L-selectin and P-selectin double knockout mice, E- and P- selectin double knockout mice and E- and P- selectin ICAM-1 triple knockout mice. The conclusions of these studies were that peripheral neutrophil numbers are regulated by a feedback loop involving G-CSF and IL-17 and that this feedback loop would be disrupted when neutrophils cannot migrate into peripheral tissues [Forlow et al., 2001]. Since there is a limit in how many genetic mutations can be generated in one strain whilst maintaining viability, additional aforementioned techniques were successfully employed. In double and triple knockout mice, IL-17 was neutralized using in vivo expression of the soluble mIL-17Fc receptor with adenovirus technology. Additional in vivo G-CSF neutralization was accomplished with administration of polyclonal antibody. Thus, different cytokine expression and knockout techniques were found complementary in these studies.

Overexpression of IL-17 has been associated with human autoimmune disease in humans, such as psoriasis, rheumatoid arthritis, or other connective tissue diseases [Albanesi et al., 2000; Homey et al., 2000; Kurasawa et al., 2000; Lubberts et al., 2000, 2001]. IL-17 may also play a role in hyper-reactivity diseases such as asthma [Linden et al., 2000; Molet et al., 2001; Wong et al., 2001]. Experimentally, autoimmune disease can be induced in animals where intraarticular adenovirus mediated mIL-17 expression leads to destructive arthritis. Its destructive role in arthritis may be related to several different independent mechanisms. IL-17 induced secondary cytokines (GM-CSF, IL-6, IL-1) stimulate osteoclast activity, which lead to bone resorption [Chabaud et al., 1998, 2001; Rifas and Avioli, 1999; Van bezooijen et al., 1999; Lenarczyk et al., 2000; Bush et al., 2001; Lubberts et al., 2000]. However, in studies by Lubberts et al. [2001] using a well-established collagen induced murine model of arthritis, IL-17 was found to cause joint destruction

independently of IL-1, a proinflammatory cytokine believed to be a major causative agent of arthritis [Lubberts et al., 2001]. IL-17 also induces matrix metalloproteinases, which can proteolytically degrade collagens and proteoglycans. Neutrophils with proteolytic enzymes are attracted into areas of increased IL-17 production and accelerate joint destruction. IL-17 was found in an animal model to enhance allograft rejection [Antonysamy et al., 1999a,b; Woltman et al., 2000; Tang et al., 2001]. In patient derived tissue samples from different autoimmune diseases, IL-17 was found to be increased: systemic multiple sclerosis [Kurasawa et al., 2000], psoriasis [Homey et al., 2000; Teunissen et al., 1998], and in some gynecological cancers [Tartour et al., 1999; Kato et al., 2001]. However, the role of IL-17 in neoplasms has not been sufficiently investigated as these data are conflicting with in vivo studies. Hirahara et al. [2000] found in their animal models IL-17 related reduced tumor proliferation and induction of tumor-specific antitumor immunity with IL-17 transduced tumors. The authors concluded the mechanism to be via augmenting the expression of MHC class I and II antigens [Hirahara et al., 2000, 2001].

Whilst IL-17 overexpression maybe linked to disease, lack of IL-17 could also be associated with pathology in humans. However, only empiric observational evidence is available which is derived from patients with T-cell deficiencies. For instance, AIDS patients are characterized by progressive loss of memory T-cells. Cytotoxic chemotherapy with drugs such as fludaribine or chronic alcohol consumption can result in decrease and functional T-cell deficiency. All these conditions are associated with significantly impaired microbial host defense, specifically with bacterial pneumonias. The incidence of trilineage bone marrow failure in AIDS patients is inversely related to the T-cells count [Moses et al., 1998]. Although these clinical observations are intriguing, caution is warranted regarding their interpretation, as T-cell deficiency syndromes do not conclusively establish the role of IL-17 in humans.

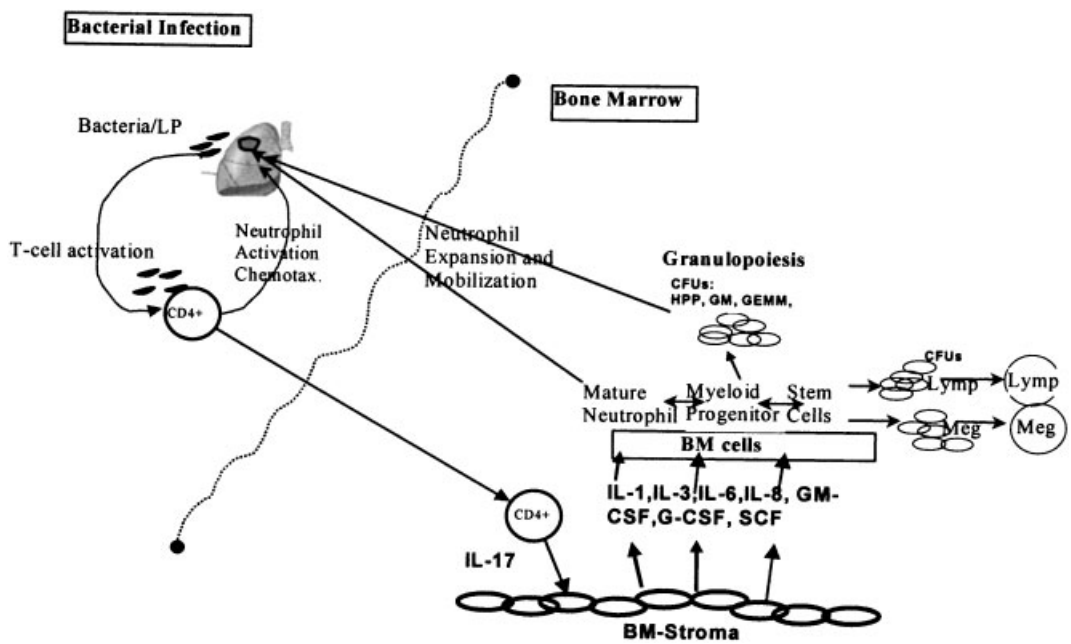

Fig. 3. Proposed model for IL-17 actions in vivo. During microbial infection (e.g. pneumonia), bacterial products directly induce in T-cells IL-17 expression. We propose several key functions of IL-17 and actions upon the microenvironment of the infected tissue and also within the microenvironment of hematopoietic organs: IL-17 A) activates local neutrophils via the release of secondary cytokines (G-CSF, IL-8, stem cell factor) and B) recruits additional neutrophils to the inflamed tissue. Activated T-cells also migrate and interact within hematopoietic organs to C) demarginate pooled neutrophils. Bone marrow stroma cells are stimulated via IL-17 to secrete hematopoiesis stimulating cytokines, specifically stimulating formation and proliferation of myeloid precursors (D). These actions secure the immediate activation and recruitment of localized neutrophils within the affected tissue, and also the sustained proliferation of granulocytes from hematopoietic organs to effectively combat bacterial infections.

Our proposed model views IL-17 as a critical response cytokine which is essential for microbial host defense. By migrating activated T-cells, communication to reservoirs of mature and precursor myeloid host defense cells, mainly neutrophils, can be established. Locally, IL-17 is required for neutrophil attraction and activation, where secondary cytokines and chemokines are released from fibroblasts and connective tissue. Within the hematopoeitic microenvironment bone marrow stroma cells are mediating effects via release of secondary cytokines and modulation of adhesion molecules. IL-17 is not only required during the immediate stress response, but also to sustain proliferation and stimulation of short-lived neutrophils. Our proposed model of IL-17 in vivo actions and interactions are depicted in Figure 3.

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