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3. Cytokines and chemokines

John W. Steinke, PhD, and Larry Borish, MD *Charlottesville, Va*

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Cytokines and chemokines are secreted proteins with growth, differentiation, and activation functions that regulate the nature of immune responses. Cytokines are involved in nearly every facet of immunity and inflammation, from induction of the innate immune response to the generation of cytotoxic T cells and the development of antibodies by the humoral immune system. The combination of cytokines that are produced in response to an immune insult determines which arm of the immune system will be activated. For this update, recent advances in our understanding of cytokines will be discussed, which includes the IL-10, IL-17, and IL-27 families. (*J Allergy Clin Immunol* 2006;117:S441-5.)

Key words: *Interleukin, cytokine, chemokine, T cell*

EVOLUTION OF CYTOKINE BIOLOGY AND NOMENCLATURE

Identification and classification of cytokines has undergone 3 phases of development. Initially, cytokines were identified purely by their biologic activities and termed *factors*, reflecting that activity (eg, T-cell growth factor). The development of cloning strategies and the ability to generate purified recombinant proteins (eg, IL-2) led to the recognition of how confused the factor phase was, with the recognition of the tremendously pleiotropic and redundant activities of cytokines. Subsequently, cytokines were identified on the basis of their unique expression patterns, such as in activated T helper lymphocytes. This *recombinant cloning* phase led to much of our current understanding of cytokines. However, cytokine biology has now evolved into a third phase driven primarily by genomics and, in particular, the human genome project. With the identification of the complete repertoire of human genes, a major effort is now being applied to assigning a

Abbreviations used

APC: Antigen-presenting cell
NK: Natural killer
Treg cell: Regulatory T cell

function for the huge library of previously unrecognized proteins. One of the more effective approaches to achieve this objective is through sequence comparison with previously known genes and predicting that homologous proteins should have related functions. In the current genomic phase of cytokine development, numerous candidate cytokines have been identified on the basis of their homologies to previously described cytokines. In the exact reverse of the factor phase of cytokine development, the predicted protein is expressed, and its biologic activities are assessed in a series of biologic assays. These assays include, most importantly, assessment of the phenotype of mice genetically engineered to either knock out the gene or overexpress it either locally or systemically. At present, at least 70 candidate cytokines have been proposed. After identification and consensus is achieved regarding each candidate's biologic activity, a cytokine nomenclature is assigned. For this review, recent advances in our understanding of cytokines since the 2003 *Primer on Allergic and Immunologic Diseases*¹ will be discussed and in particular the IL-17/IL-25 and IL-10 families of cytokines.

NEW MEMBERS OF THE CYTOKINE FAMILY IL-28 and IL-29

A new family of cytokines was identified after a genome search for cytokines with core sequences composed of α -helical bundles. This family is clustered on chromosome 19q13.13 and contains IL-28A, IL-28B, and IL-29.² IL-28A and IL-28B share 96% amino acid identity, whereas IL-28A and IL-29 share 81% amino acid identity. At the amino acid level, IL-28 and IL-29 appear closely related to the α/β IFNs, but the genomic organization is more similar to members of the IL-10 family. This family of cytokines signals through a heterodimeric receptor consisting of an interferon receptor subunit, IL-28R α ,

From the Asthma and Allergic Disease Center, Beirne Carter Center for Immunology Research, University of Virginia Health Systems, Charlottesville.

Reprint requests: John W. Steinke, PhD, Asthma and Allergic Disease Center, Beirne Carter Center for Immunology Research, University of Virginia Health Systems, PO Box 801355, Charlottesville, VA 22908-1355. E-mail: js3ch@virginia.edu.

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and the IL-10R α , a receptor used by many members of the IL-10 gene family. Both cytokines were shown to have antiviral properties because viral infection of a hepatocellular cell line was prevented by pretreating the cells with either cytokine. It is speculated that this new cytokine family might serve as an alternative to α/β IFNs in providing immunity to viral infection.

IL-31

A previously uncharacterized cytokine receptor related to the gp130-like type 1 family of receptors was identified on the basis of sequence homology. An immunoglobulin-type C2-like domain at the N terminus and a fibronectin domain at the C terminus characterize this family. Functional cloning was used to identify a ligand for this receptor that was termed IL-31.³ Human IL-31 maps to chromosome 12q24.31 and codes for a mature peptide of 141 amino acids containing 4 helical bundles, which suggests that it might be a member of the hematopoietin family that includes IL-3. High levels of expression were found in activated CD4⁺ T cells, with the highest levels found in T cells activated in T_H2-skewing conditions. IL-31 induces expression of a large number of chemokines without altering cytokine levels. This suggests that IL-31 alone is involved in the recruitment of polymorphonuclear cells, monocytes, and T cells to sites of inflammation. Support for this was demonstrated in 2 mouse models. The skin of transgenic mice overexpressing IL-31 showed an increase in the number of lesions with an inflammatory cell infiltrate similar to that observed in atopic dermatitis. In a mouse model of antigen-induced airway hyperreactivity, the lungs displayed increased expression of the IL-31 receptor. The potential role of this cytokine in allergic responses warrants further investigation in light of these early observations.

IL-32

In a search for IL-18-inducible genes, microarray analysis revealed induction of a cytokine-like gene that was subsequently isolated and cloned as IL-32.⁴ The gene is located on chromosome 16p13.3 and through alternative mRNA splicing can generate 4 variants. Northern blot analysis revealed the highest levels of expression in immune cells, including natural killer (NK) and T cells; however, expression could also be induced in epithelial cells by IFN- γ and IL-1 β . IL-32 is not homologous to any other known cytokine. IL-32 induces several proinflammatory cytokines, such as TNF- α , CXCL8 (IL-8), and macrophage inflammatory protein 2 from differentiated macrophages. Further studies are needed to address the role of IL-32 in inflammatory or autoimmune diseases.

CYTOKINE PRODUCTION BY ANTIGEN-PRESENTING CELLS

Cytokines primarily derived from mononuclear phagocytic cells and other antigen-presenting cells (APCs) are

effective in promoting the cellular infiltrate and tissue damage characteristic of inflammation. Processing of antigens as they are taken up by APCs, metabolized, and presented to T helper lymphocytes provides one pathway for this class of cytokine production. Alternatively, monocytes are potentially triggered to produce cytokines through the innate immune system using pattern recognition receptors that recognize stereotypic components of pathogens that do not occur on mammalian cells. These receptors, which include the Toll-like receptor family, contribute to the ability of the immune system to distinguish pathogenic from nonpathogenic proteins. The cytokines predominantly produced by monocytes include TNF, IL-1, IL-6, CXCL8 (IL-8) and other members of the chemokine family, IL-12, IL-15, IL-18, IL-23, and, as described since the previous review,¹ IL-27.

The cells responsible for most of the IL-27 production are macrophages and dendritic cells. Early studies indicated that IL-27 can function as a proinflammatory cytokine because it synergizes with IL-12 to induce IFN- γ production from human NK cells and to promote T_H1 responses. T_H1 immune deviation is due in part to the induction of T-bet, a transcription factor that targets genes involved in the T_H1 response. Similar to IL-12, ligation of the IL-27 receptor also activates the signal transducer and activator of transcription 4 signaling pathway in naive CD4⁺ T cells to push them into a T_H1 phenotype. IL-27 signals through a heterodimeric receptor consisting of the IL-27 receptor and gp130. As has been observed with other members of the IL-6/IL-12 family, IL-27 also has anti-inflammatory properties. In mice deficient for the IL-27 receptor, there was increased proliferation of CD4⁺ T cells that was independent from the effect on T_H1 immune deviation. Addition of recombinant IL-27 to naive T cells in culture under T_H2-polarizing conditions results in decreased expression of GATA-3, a transcription factor important for T_H2 development. Concurrent with the decrease in GATA-3 was a decrease in IL-4 production. The decrease in T_H2 cytokines caused by IL-27 is a result of inhibition of T_H2 cell development. These results suggest that IL-27 might serve a dual role in T-cell development and the immune response by stimulating production of T_H1 responses while inhibiting production of T_H2 inflammatory responses. It remains to be determined whether this property can be exploited to alter the allergic phenotype.⁵

CELLULAR IMMUNITY

Cellular immunity describes any adaptive immune response in which antigen-specific T cells have a role. These immune responses are characterized by the clonal selection and expansion of antigen-specific lymphocytes that serve as effector cells to eliminate pathogens and generate memory cells for long-term resistance to disease. Many cytokines are involved in cell-mediated immunity, including IL-2, IL-15, IL-16, IL-21, TNF- β , and IFN- γ .¹ Important roles in cellular immunity have

also recently been ascribed to members of the IL-17 family.

The original member of this family, IL-17A, was first identified in 1995 and had no known sequence similarity to any other cytokine or mammalian protein. Since this time, 5 other members of this family have been cloned: IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F. Family members have a molecular weight of 20 to 30 kD, with overlapping but not identical biologic activities. All have 4 conserved cysteine residues, and the crystal structure of IL-17F shows that these residues are involved in forming a cysteine knot (a structure involving disulphide bonds between cysteine residues that exposes hydrophobic residues and leads to protein dimerization), a common motif found in many growth factors. Cell sources for these cytokines are distinct. IL-17A is mainly expressed in CD4⁺ T cells after activation and to a lesser extent from neutrophils, eosinophils, and CD8⁺ T cells. The cellular sources for IL-17B and IL-17C have not been determined. In contrast to IL-17A, IL-17D is expressed in resting CD4⁺ T cells and at low levels from B cells. The expression of IL-17E is restricted to T_H2 cells, and as discussed below, it might be involved in the allergic response. Similar to IL-17A, IL-17F is expressed in activated CD4⁺ T cells, but it can also be expressed in activated basophils and cord blood-derived mast cells, suggesting a wider tissue distribution.⁶

Both IL-17A and IL-17F can induce expression of a variety of cytokines and chemokines from epithelial and vascular endothelial cells, including IL-6, granulocyte colony-stimulating factor, GM-CSF, and CXCL10 (interferon-inducible protein-10 [IP-10]). The neutrophil-activating factors IL-6 and CXCL8 (IL-8) are secreted by fibroblasts in response to both cytokines. The ability to induce neutrophil migration but not eosinophil migration makes it likely that these cytokines play an important role in severe persistent asthma and chronic obstructive pulmonary disease, in which accumulation of neutrophils in the airways is a hallmark of disease. One of the shared characteristics of these diseases and asthma is airway remodeling marked by subepithelial fibrosis. IL-17A can additionally induce expression of the profibrotic cytokines IL-6 and IL-11, whereas IL-17F can induce TGF- β expression by human endothelial cells. Both cytokines share the ability to induce goblet cell hyperplasia and mucus hypersecretion. The data describing IL-17E (IL-25) involvement in asthma are more convincing. Overexpression of IL-17E results in airway eosinophilia and increases in serum levels of IL-5, IL-13, and IgE. The increases in cytokine levels are directly related to the ability of IL-17E to induce these genes in T_H2 cells. IL-17E is also unique in that it can increase expression of CC chemokines, such as CCL5 (RANTES) and CCL11 (eotaxin 1), which might explain the homing of eosinophils to the lungs.⁶ Because of the functionality of this cytokine family, therapeutic agents targeting these genes offer new approaches to treatment of lung diseases.

ANTI-INFLAMMATORY CYTOKINES

In addition to cytokines that stimulate cytotoxic, cellular, humoral, and allergic inflammation, several cytokines have predominantly anti-inflammatory effects including IL-1Ra, TGF- β , and IL-10. Since our previous published cytokine summary,¹ the biology of the IL-10 family has been further defined and extended to include several new members.

IL-10 family: IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26

IL-10 is a product of numerous cells, including T_H1 and T_H2 lymphocytes, cytotoxic T cells, B lymphocytes, mast cells, mononuclear phagocytic cells, and dendritic cells. The primary T-cell source for IL-10 is regulatory T lymphocytes, as discussed below. However, monocytes and B cells are the major sources of IL-10 in human subjects. IL-10 inhibits production of IFN- γ and IL-2 by T_H1 lymphocytes; IL-4 and IL-5 by T_H2 lymphocytes; IL-1 β , IL-6, CXCL8 (IL-8), IL-12, and TNF- α by mononuclear phagocytes; and IFN- γ and TNF- α by NK cells. In addition, IL-10 inhibits MHC class II, CD23, intercellular adhesion molecule 1, and CD80/CD86 expression by dendritic cells and other APCs. Inhibition of CD80/CD86 expression eliminates the ability of the APC to provide the accessory signals necessary for T helper activation, and this is primarily responsible for the inhibition of T_H1 and T_H2 cytokine production. Constitutive expression of IL-10 by immature dendritic cells and mononuclear phagocytic cells in the respiratory tract of healthy subjects has a critical role in the induction and maintenance of tolerance to allergens and otherwise benign bioaerosols. In contrast, asthma and allergic rhinitis are associated with diminished IL-10 expression in the allergic airway by both alveolar macrophages and dendritic cells, which contributes to the development of an inflammatory milieu,⁷ reflecting in part the presence of mature dendritic cells. Further support for a modulating role of IL-10 in human allergic disease is derived from observations that IL-10 inhibits eosinophil survival and IL-4-induced IgE synthesis. These inhibitory effects of IL-10 are in contrast to its effect on B lymphocytes, in which it functions as an activating factor that stimulates cell proliferation and immunoglobulin secretion. IL-10 enhances isotype switching to IgG4 and functions as a growth cofactor for cytotoxic T cells. Thus IL-10 inhibits cytokines associated with cellular immunity and allergic inflammation while stimulating humoral and cytotoxic immune responses.

Newer members of the IL-10 family include IL-19, IL-20, IL-22, IL-24, and IL-26. As discussed above, it is likely that IL-28 and IL-29 also belong to the same subfamily. These cytokines and their receptors loosely share homologies with IFN/IFN receptors and display antiviral activity. In contrast to IL-10, none of these cytokines significantly inhibits cytokine synthesis, an activity that remains unique for IL-10.

IL-19 shares 21% amino acid identity with IL-10 and has similar exon-intron structure. Its expression by

TABLE I. CD4⁺ T cells with regulatory activity

Regulatory T cell	Characteristic
Treg	• CD25⁺ foxp3⁺ thymus derived • Not dependent on IL-10 for biologic activity • Mediate self-tolerance/prevent autoimmune disease • Not likely to be relevant to acquired tolerance to allergens
T _H 3	• Characterized by TGF-β (± IL-10) production • Mediate mucosal tolerance/antigen-specific IgA production • Not relevant to allergy or immunotherapy
T _R 1	• Peripheral-derived regulatory T cells • IL-10 responsible for their biologic activity (± TGF-β) • Possibly derived from T_H1-like/T_H2-like lymphocytes or natural T cells • ± CD25 expression (reflecting their effector function-activation) • Foxp3 negative • Proposed mechanism of immunotherapy efficacy

monocytes is induced by LPS.⁸ IL-19 activates monocytes to secrete the cytokines IL-6 and TNF-α and produce reactive oxygen species. It is upregulated by IL-4 and GM-CSF and downregulated by IFN-γ. Consistent with a positive feedback loop, in the presence of IL-19, increased numbers of IL-4 and fewer IFN-γ-producing cells are observed, thus promoting T_H2 immune deviation.^{9,10} Serum levels of IL-19 in asthmatic subjects are twice those seen in healthy control subjects and correlated with increased levels of IL-4 and IL-13 in the serum. Increased expression in murine models further suggests a role in asthma.¹⁰

IL-20, another recently described member of the IL-10 family, is predominantly expressed by monocytes and skin keratinocytes and is overexpressed in patients with psoriasis. It induces keratinocyte proliferation, and overexpression in mice is lethal after defective skin formation.

IL-22 is derived from T lymphocytes and mast cells, and its expression is induced by IL-9 and LPS. The predominant biologic activity described for IL-22 is induction of acute-phase responses in hepatocytes, including serum amyloid A protein. Consistent with the IFN-like activities of these cytokines, it induces MHC class I antigen expression.⁸

IL-24 is the fourth new member of the IL-10 family and is produced by monocytes and T_H2 lymphocytes in an IL-4-inducible fashion. It induces tumor apoptosis.⁸

Finally, IL-26 is primarily generated by monocytes and memory cells and is considered important in the transformation of human T cells after their infection by herpes virus saimiri.¹¹ This might be analogous to the role of IL-10 in EBV-mediated B-cell transformation. Engagement of the IL-26 receptor is associated with induction of CXCL8 (IL-8) and IL-10, as well as cell surface expression of CD54 (intercellular adhesion molecule 1). It is located in the chromosome 12q15 gene cluster, along with IFN-γ and IL-22, in an area thought to contribute to allergic and autoimmune diseases. In contrast, IL-19, IL-20, and IL-24 cluster into the IL-10 region on chromosome 1.

These cytokines have unique heterodimer receptor components, which are shared. For example, IL-19, IL-20, and IL-24 share the IL-20Rα/IL-20Rβ (type I IL-20R) receptor. IL-22 has a unique receptor, and IL-20 and IL-24 (but not IL-19) can also use this IL-22Rα/IL-20Rβ receptor (type II IL-20R). A soluble form of the IL-22 receptor functions as a natural antagonist for IL-22 (IL-22-binding protein). Interestingly, the IL-22-binding protein is quite specifically expressed by dendritic cells.¹² IL-26 has a unique receptor consisting of a heterodimer of the IL-22Rα chain and the IL-10Rβ chain.¹³ All of these receptors have unique patterns of expression, which determine in part their unique activities. In contrast to IL-10 receptors, IL-20Rα, IL-20Rβ, and IL-22R are absent or expressed at extremely low levels on cells of the hematopoietic lineage. These receptors are mainly found on epithelial cells, stromal cells, and fibroblasts of various tissues.

IL-10 and regulatory T-lymphocyte families

In addition to traditional T_H1 and T_H2 subclasses of helper lymphocytes described in the previous review,¹ much progress has been made in the past several years in identifying and clarifying the characteristics and functions of several families of regulatory T lymphocytes, at least in murine systems (Table I). These include IL-10-producing lymphocytes (termed T_R1 cells), CD25⁺ regulatory T cells (Treg cells), and TGF-β (± IL-10)-producing T_H3 cells. Thymus-derived Treg cells are characterized by their constitutive expression of the IL-2 receptor (CD25) and the transcription factor foxp3. They are produced in response to thymic expression of self-antigens and are important for prevention of autoimmunity. T_H3 cells are primarily gut derived, and their function is ascribed to mucosal tolerance. Reflecting their prominent production of TGF-β, in addition to tolerance, they are relevant to antigen-specific IgA production. Although critically important for self-tolerance and mucosal immunity, respectively, these cell types are less likely to be involved in either tolerance to allergens in healthy subjects or the immune benefits associated with allergen immunotherapy. In contrast, induction of IL-10-producing T_R1 cells might play a key role in reducing allergen-specific T-cell responsiveness in healthy subjects and after immunotherapy. A prominent role of IL-10-producing CD4⁺ cells was first described in studies involving bee venom immunotherapy.¹⁴ Subsequent investigations have extended the importance of IL-10 (and TGF-β) production by CD4⁺ T cells to inhalant allergy¹⁵ and confirmed that this occurred in parallel to suppression of T_H2-proliferative responses and cytokine production.¹⁶ In this latter study, IL-10 responses in healthy nonatopic individuals exposed to allergen were similar to those in the immunotherapy-treated group, implying restoration of tolerant T-cell responses in the atopic individual. However, this area of research remains confused. For example, although a role for CD25 expression has been ascribed to these IL-10-producing cells, it is unclear whether this reflects the constitutive expression of this component of the IL-2 receptor, the signature

characteristic of Treg cells, or, more likely, activation of effector T cells. Similarly, although termed T_H1 cells, the origins of these cells remain obscure, including whether they represent a unique developmental pathway or, more likely, a differentiation pathway of preexisting T helper lymphocytes. However, what is consistent is that each of these studies has found cells capable of making high levels of IL-10 ($\pm$ TGF- β) consistent with the T_H1 cell type, and current concepts focus on the integral role of these IL-10-producing cells in immune tolerance to allergens in healthy subjects and after immunotherapy.

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4. Autoimmunity, vasculitis, and autoantibodies

Susan J. Lee, MD, and Arthur Kavanaugh, MD *San Diego, Calif*

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Autoimmune diseases are distinct clinical syndromes characterized by various alterations in normal immune responsiveness, such that there is a loss of tolerance to particular host constituents. In most cases, despite years of intense investigation, the etiopathogenic antigens initiating these systemic inflammatory conditions remain undefined. However, a great deal has been learned about the changes in components of the immune response relevant to the propagation and sustenance of these often chronic disorders. In addition, various hormonal, environmental, physiologic, and other influences that affect their expression have been identified. The expression and ultimate clinical outcome of autoimmune diseases usually relate to inflammation-related damage to the target organ with subsequent dysfunction. Certain immune conditions, such as autoimmune thyroid disease, largely affect a single organ, whereas others, such as systemic lupus erythematosus, heterogeneously affect sundry organ systems. Autoantibodies directed against normal host

antigens are a common feature of many autoimmune diseases. In some cases they are pathogenic, whereas in others they serve as markers for organ involvement or outcomes. Clinical descriptions of autoimmune diseases date back many decades in some cases. Recent efforts at formulating classification criteria have allowed clearer distinctions and more accurate stratification. Greater understanding of the immunopathogenesis of autoimmune conditions has led to the development and introduction into the clinic of novel immunomodulatory therapies and treatment paradigms that have substantially improved the outcomes for patients affected by these serious conditions. (*J Allergy Clin Immunol* 2006;117:S445-50.)

Key words: Rheumatoid arthritis, systemic lupus erythematosus, vasculitis, autoantibodies

Autoimmune diseases are characterized by dysregulation in various components of immune response. Traditionally, they have been categorized as either cell mediated, with a particular role for T_H1 T cells, or humoral, with autoantibodies playing a key role in certain disease manifestations. In addition, it is now understood that components of the inflammatory responses (eg, cytokines) might be relevant and common to tissue damage in diverse autoimmune conditions. With a greater understanding of pathogenesis coupled with the advances in

From the Division of Rheumatology, Allergy, and Immunology, and the Center for Innovative Therapy, the University of California, San Diego.

Reprint requests: Arthur Kavanaugh, MD, University of California, San Diego, San Diego, California, 9500 Gilman Dr, La Jolla, CA 92093-0943. E-mail: akavanaugh@ucsd.edu.

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