

The extended IL-10 superfamily: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29

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Cytokines are involved in virtually every aspect of immunity and inflammation. A cascade of responses evolves after cytokine activation, although optimal function might ultimately involve several complementary cytokines. Understanding the function of individual cytokines is complicated because their role can vary depending on the cellular source, target, and phase of the immune response. In fact, numerous cytokines have both proinflammatory and anti-inflammatory potential, with the contrasting outcome observed being determined by the immune cells present and their state of responsiveness to the cytokine. These issues make the study of cytokine biology daunting, particularly so for IL-10 and IL-10-related genes. The IL-10 superfamily is highly pleiotropic. These genes are linked together through genetic similarity and intron-exon gene structure. Significant commonality exists not only through shared receptors but also through conserved signaling cascades. However, its members mediate diverse activities, including immune suppression, enhanced antibacterial and antiviral immunity, antitumor activity, and promotion of self-tolerance in autoimmune diseases. (J Allergy Clin Immunol ■■■■;■■■: ■■■-■■■.)

Key words: IL, cytokine, IL-10-related cytokines

Cytokines are involved in virtually every aspect of immunity and inflammation. Not only do cytokines determine whether a response occurs after an immune insult, the production of particular cytokines subsequently determines the nature of the response (cytotoxic, humoral, cell mediated, or allergic) or, in contrast, nonresponsiveness and active immune suppression. A cascade of responses evolves after cytokine activation, although optimal function might ultimately involve several complementary cytokines. Understanding the function of individual cytokines is complicated because their role can be variable depending on the cellular source, target, and phase of the immune response during

Abbreviations used

APC: Antigen-presenting cell
DC: Dendritic cell
Jak: Janus kinase
STAT: Signal transducer and activator of transcription

which they function. In fact, numerous cytokines have both proinflammatory and anti-inflammatory potential, with the contrasting outcome observed being determined by the immune cells present and their state of responsiveness to the cytokine. These issues make the study of cytokine biology daunting, particularly so for IL-10 and IL-10-related genes. For this review, updates in our understanding of the extended IL-10 family will be discussed.

IL-10

IL-10 is an important immunoregulatory cytokine with multiple biologic effects on different cell types. Although the primary T-cell source for IL-10 is regulatory T lymphocytes, monocytes and B cells are the major sources of IL-10 in human subjects.¹ IL-10 forms a homodimer and exerts its biologic function through the IL-10R1 and IL-10R2 receptor complex, with subsequent activation of Janus kinase (Jak) 1 and tyrosine kinase 2, signal transducer and activator of transcription (STAT) 1, and STAT3 (Table I). Other kinases, including mitogen-activated protein kinase and enzymes (heme oxygenase-1) are likely also involved in IL-10 signaling. 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 natural killer cells. Monocyte MHC class II molecule expression is inhibited by IL-10, as is expression of CD23 (low-affinity IgE receptor, Fc ϵ R2), intracellular adhesion molecule 1, and CD80 (B7.1)/CD86 (B7.2). IL-10 inhibition of expression of the important costimulatory molecules CD80 and CD86 by dendritic cells (DCs) and other antigen-presenting cells (APCs) eliminates the ability of the APC to provide the accessory signals necessary for T_H cell activation. This inhibition of accessory function is primarily responsible for the inhibition of T_H1 and T_H2 cytokine production. Notably, recent studies have also indicated that IL-10 functions directly on T cells to inhibit their cytokine production by suppressing expression of the T cell–costimulatory molecules CD28 and inducible T-cell costimulator, thereby regulating their threshold of T-cell activation.²

Growing evidence supports a modulating role for IL-10 in human allergic disease. Constitutive expression of IL-10 by APCs in the respiratory tract of healthy subjects has a crucial role in the induction and maintenance of tolerance to allergens, whereas

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TABLE I. IL-10 superfamily: receptors and signaling

Member	1° Cell source	Receptor	Activated signal transducer
IL-10	Monocytes, B cells, regulatory T lymphocytes	IL-10R1/IL-10R2	Jak1, tyrosine kinase 2, STAT1, STAT3
IL-19	Monocytes	IL-20R1/IL-20R2	STAT1, STAT3
IL-20	Monocytes, skin keratinocytes	IL-20R1/IL-20R2, IL-22R1/IL-20R2	Jak/STAT
IL-22	Activated T cells, activated natural killer cells, T _H 17 cells	IL-22R1/IL-10R2	STAT3 (keratinocytes)
IL-24	Melanocytes, monocytes, T _H 2 lymphocytes	IL-20R1/IL-20R2, IL-22R1/IL-20R2 (skin only)	STAT3
IL-26	Monocytes, memory T cells	IL-20R1/IL-10R2	STAT1, STAT3
IL-28, IL-29	DCs	IFNLR1/IL-10R2	Jak1, STAT1, 2, 3 and 5

TABLE II. IL-10 superfamily: biologic effects and clinical effect

Member	Biologic effect	Clinical association
IL-10	Immune suppression, anti-inflammatory	Burkitt lymphoma, malignant B-cell lymphomas
IL-19	Skin development, immunoregulatory	Psoriasis, asthma
IL-20	Skin development and inflammation, hematopoiesis	Psoriasis, atherosclerosis, angiogenesis
IL-22	Acute-phase response, innate immunity	Crohn's disease, interstitial lung disease, rheumatoid arthritis, psoriasis
IL-24	Proapoptosis, epidermal functions, inflammatory cascade	Melanoma, psoriasis, inflammation
IL-26	Mucosal and cutaneous immunity	T-cell transformation
IL-28, IL-29	Antiviral immunity	Hepatitis B/C infection

asthma and allergic rhinitis are associated with diminished IL-10 expression in the allergic airway.³ This diminished IL-10 expression is thought to contribute to the development of an inflammatory milieu, reflecting in part the presence of mature DCs. IL-10 has inhibitory effects on eosinophil survival and IL-4-induced IgE synthesis; however, in B lymphocytes it functions as an activating factor that stimulates cell proliferation and immunoglobulin secretion. IL-10 augments 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 responses (Table II). More detailed reviews of the biology of IL-10 can be found elsewhere.^{4,5}

IL-19

IL-19 was discovered in 2000 and was found to share 21% amino acid identity with IL-10, but as with other members of the IL-10 superfamily, it is their similar exon-intron structure that primarily defines their homology. Within the immune system, IL-19 is primarily produced by monocytes, and its expression can be induced by LPS, IL-4, and GM-CSF. IL-19 signals through a receptor complex composed of the IL-20R1 and IL-20R2 chains and activates monocytes in an autocrine and paracrine fashion to release the cytokines IL-6, TNF- α , and numerous reactive oxygen species. Monocyte IL-19 production is downregulated by IFN- γ .

Roles for IL-19 have primarily been investigated in psoriasis and allergic disorders. IL-19 is found in the suprapapillary basal layer of healthy skin. Patients with psoriasis have increased levels of IL-19 in basal and suprabasal keratinocytes of involved skin, where it is thought to contribute to the inflammatory process. Human CD8⁺ T cells exposed to IL-19 induced keratinocyte growth factor, and in a positive feedback loop, keratinocyte growth factor-responsive elements in the *IL-19* promoter increase expression of IL-19. Cyclosporine decreases IL-19 expression, and this might explain some of the utility of this drug in the treatment of psoriasis (Table II).

IL-19 is capable of promoting T_H2 immune deviation through a positive feedback loop, resulting in increased numbers of IL-4-producing and fewer IFN- γ -producing cells.^{6,7} Consistent with a role for IL-19 in asthma, serum levels of IL-19 in asthmatic patients were found to be twice those of the healthy control subjects and correlated with higher levels of IL-4 and IL-13 in the serum.⁶

IL-20

The human *IL-20* gene maps to a 195-kb region on chromosome 1q32 that also includes *IL-10*, *IL-19*, and *IL-24*.⁸ Although part of the same family, IL-20 has diverged to a large extent from IL-10 in sequence and function. The amino acid sequences of IL-20 and IL-10 are only 28% identical, and the recombinant human IL-20 protein seems to form a monomer instead of the intercalating dimer characteristic of IL-10.⁸ Although multiple cell types express IL-20, it is predominantly expressed by monocytes and skin keratinocytes. IL-20 protein is also found at high levels in the skin of patients with psoriasis. Overexpression of IL-20 in mice is lethal secondary to defective skin formation. Similar to IL-19, IL-20 signals through the IL-20R1/IL-20R2 heterodimer; however, IL-20 also binds to the receptor complex composed of IL-22R1 and IL-20R2 (Table I). Each of these heterodimer receptor complexes functions partly through the Jak-STAT pathways. In addition to a role in psoriasis, IL-20 has been found in higher concentrations in synovial fluid from patients with rheumatoid arthritis.⁹ Other studies have also suggested a potential role for IL-20 in atherosclerosis and angiogenesis (Table II).^{10,11}

IL-22

IL-22 expression is found in activated T cells and, at lower levels, in activated natural killer cells.¹² Among T-lymphocyte subsets, IL-22 is preferentially expressed by CD4⁺ T_H cells. No expression of IL-22 has been found in macrophages, mature or immature DCs, or nonimmune cells.¹³ The preferential

production of IL-22 by T cells suggests that increased levels of this cytokine might exist in T lymphocyte-mediated diseases. Notably, psoriasis, Crohn's disease, interstitial lung diseases, and rheumatoid arthritis all have evidence of increased levels of IL-22 protein or mRNA transcripts, and these correlate with disease severity (Table II).¹⁴⁻¹⁶ The IL-22 receptor complex is a heterodimer consisting of the IL-22R1 and IL-10R2 chains (Table I). Neither resting nor stimulated immune cells express IL-22R1, and therefore despite its structural similarity to IL-10, immune cells are not the target cells of IL-22. The pattern of IL-22R1/IL-10R2 expression suggests that the most important cellular targets of IL-22 are found within the skin, kidney, respiratory, and digestive systems. Given that these target cells are located in tissues that are in contact with the environment and that IL-22 leads to the production of antimicrobial peptides, IL-22 is presumed to play an important role in innate pathogen defense. IL-22 also induces acute-phase reactants in hepatocytes and likely possesses a protective role in liver injury. Complicating the matter is the uncertain role that the IL-22 binding protein, a secreted soluble decoy receptor, might have in modulating IL-22 effects. Another postulated function of IL-22 binding protein includes temporary sequestration of IL-22 to prolong its half-life, possibly facilitating the arrival of IL-22 at remote parts of the body.

IL-24

Originally identified as a tumor suppressor molecule (melanoma differentiation-associated gene 7) that was expressed in healthy melanocytes but not metastatic melanoma cells, melanoma differentiation-associated gene 7 was subsequently discovered to have a chromosomal location within the *IL-10* locus with which it shares structural and sequence homology and is now termed *IL-24*. It is produced by monocytes and T_H2 lymphocytes in an IL-4-inducible fashion. IL-24 signals through a heterodimer consisting of the IL-20R1 and IL-20R2 chains, leading to activation of STAT3 (Table I). IL-24 promotes secretion of TNF- α and IL-6 from human monocytes. Its potential role as a cancer therapeutic is derived from evidence that IL-24 induces antitumor immune responses with significant independent "bystander" antitumor effects (Table II).^{17,18} In addition, IL-24 promotes apoptosis of tumor cells without apparently targeting nonneoplastic tissue. Jak/STAT activation is not involved in apoptotic signaling because Jak/STAT knockout mice still demonstrate apoptosis of tumor cells after exogenous IL-24 addition. Current investigations are focused instead on the unique expression of the intracellular chaperone molecule GRP78/BiP by cancerous cells, which might play a role in their susceptibility to apoptosis. Given the apparently ubiquitous apoptotic effect on malignant cells, the lack of an effect on normal cells, and the absence of significant side effects (eg, cytokine storm), IL-24 is a potentially important candidate cancer therapeutic, and early-phase I/II studies have shown promise.

IL-26

In contrast to *IL-19*, *IL-20*, and *IL-24*, *IL-26* is located on chromosome 12q15, where it clusters with *IL-22* and *IFN- γ* . IL-26 is primarily generated by monocytes and memory T cells. It is considered important in the transformation of human T cells after their infection by herpes virus saimiri.¹⁹ The herpes virus saimiri/IL-26 interaction exhibits shared features with the role of the similar herpesvirus, EBV, in B-cell transformation. Similar to

IL-10, IL-26 forms homodimers. IL-26 has a unique receptor consisting of a heterodimer of the IL-20R1 chain and the IL-10R2 chain (Table I).²⁰ Binding of the IL-26 receptor leads to phosphorylation of both STAT1 and STAT3 and induction of CXCL8 (IL-8), IL-10, and intracellular adhesion molecule 1 (ICAM-1).

IL-28 AND IL-29

IL-28A and IL-28B, alternatively named IFN- λ 2 and IFN- λ 3, belong, with IL-29 (IFN- λ 1), in a new cytokine family that shares with type I IFNs the same Jak/STAT signaling pathway. IFN- λ s exhibit several common features with type I IFNs, including antiviral, antiproliferative, and antitumor activities. Despite significant amino acid homology with type I IFNs, the intron-exon structure of the *IFN- λ* family genes more closely resembles that of *IL-10*.²¹ Moreover, IFN- λ s act through a cell-surface receptor composed of 2 chains, one being IFN- λ specific (IFN- λ R1) and the second, IL10R2, being shared among IL-10, IL-22, and IL-26. The gene encoding *IFN- λ R1* is located on human chromosome 1, which is in close proximity to the gene encoding the *IL-22* receptor. In addition to the mRNA encoding the full-length *IFN- λ R1*, 2 splice variants have been identified in human cells.²¹ One variant encodes a receptor with a deletion of 29 amino acids in its intracytoplasmic portion, likely disabling its signaling capacity, thus suggesting decoy function. The second variant encodes only the ectodomain, which is likely a secreted (soluble) receptor.²¹ The ratio of the 2 receptor variants will determine whether a given cell signals in response to the cytokine.

Although IL-10R2 is ubiquitously expressed, IFN- λ R1 appears to be more tightly regulated. The mRNA encoding IFN- λ R1 is undetectable in fibroblast and endothelial cells.²¹ Monocytes freshly isolated from human blood do not express IFN- λ R1, but its expression can be induced when they differentiate into DCs after IL-4 and GM-CSF treatment. IFN- λ R1 is expressed in cell lines from various tumors. Initial work showed that all IFN- λ subtypes were induced on infection of HeLa, HuH7, or HT29 cell lines by Dengue virus, Sindbis virus, vesicular stomatitis virus, or encephalomyocarditis virus supporting a role in antiviral immunity.^{21,22} Subsequent work has shown that other viruses are also capable of inducing IFN- λ expression.

Similar to type I IFNs, IL-28 and IL-29 (IFN- λ s) induce the activation of the Jak/STAT signaling pathways that variously lead to phosphorylation of STAT1, STAT2, STAT3, STAT4, and STAT5.²²⁻²⁴ Jak1, in particular, has been shown to be critical in mediating IFN- λ -induced STAT phosphorylation.²³ Evidence suggests that STAT2 is the crucial STAT in establishing type I IFN activity because it is specifically recruited in the cascade leading to IFN-stimulated response element promoter activity.²⁵ IFN- λ induces homodimers of STAT2 capable of recognizing both the IFN-stimulated response element and IFN- γ activation site sequences. It is therefore not surprising that many genes whose expression is classically induced by both type I IFNs and IFN- γ are also induced by IFN- λ s. One notable difference between IFN- λ and type I IFNs is that IFN- λ shifts immature DCs toward a program characterized by the ability to produce Foxp3-expressing CD4⁺CD25⁺ regulatory T cells. In fact, recent studies performed with a mixed lymphocyte reaction show that IFN- λ -treated DCs induce IL-2-dependent proliferation of CD4⁺CD25⁺Foxp3⁺ innate regulatory T cells. Hence IFN- λ s are able to generate tolerance-inducing DCs.²⁶

By definition, an IFN must be able to "interfere" with viral replication. As discussed above, IFN- λ indeed exhibits antiviral

activities. Of note, IFN- λ inhibits hepatitis B and C virus replication (Table II).²⁷ This observation could be important because IFN- λ might be an alternative to IFN- α for the treatment of HCV-infected patients displaying resistance to IFN- α , especially if their resistance is due to type I IFN dysfunction.²⁸ Data from recent studies suggest that the *in vivo* antiviral activity of IFN- λ is exerted on the immune system rather than preventing the cells from becoming infected.²⁹ Moreover, IFN- λ s exert an *in vivo* antitumor effect similar to that of type I IFNs that is likely mediated by an action on tumor immune surveillance rather than through its antiproliferative activity on tumor cells.³⁰ To date, there is no described phenotype associated with defective IFN- λ production on signaling except one single nucleotide polymorphism in the gene encoding *IFN- λ RI* that might be associated with susceptibility to allergic rhinitis.³¹

CONCLUSION

The IL-10 superfamily is highly pleiotropic. Its members are linked together through genetic similarity and intron-exon gene structure. Significant commonality exists not only through shared receptors but also through conserved signaling cascades. However, its members mediate diverse activities, including immune suppression, enhanced antibacterial and antiviral immunity, antitumor activity, and promotion of self-tolerance in autoimmune diseases.

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