Interleukins, from 1 to 37, and interferon-γ: Receptors, functions, and roles in diseases

Mübeccel Akdis, MD, PhD, Simone Burgler, PhD, Reto Crameri, PhD, Thomas Eiwegger, MD, Hiroyuki Fujita, MD, PhD, Enrique Gomez, PhD, Sven Klunker, PhD, Norbert Meyer, MD, Liam O'Mahony, PhD, Oscar Palomares, PhD, Claudio Rhyner, PhD, Nadia Quaked, PhD, Anna Schaffartzik, PhD, Willem Van De Veen, MSc, Sabine Zeller, PhD, Maya Zimmermann, PhD, and Cezmi A. Akdis, MD *Davos, Switzerland*

Advancing our understanding of mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumor development, organ transplantation, and chronic infections could lead to effective and targeted therapies. Subsets of immune and inflammatory cells interact via ILs and IFNs; reciprocal regulation and counter balance among T_H and regulatory T cells, as well as subsets of B cells, offer opportunities for immune interventions. Here, we review current knowledge about ILs 1 to 37 and IFN-γ. Our understanding of the effects of ILs has greatly increased since the discoveries of monocyte IL (called IL-1) and lymphocyte IL (called IL-2); more than 40 cytokines are now designated as ILs. Studies of transgenic or knockout mice with altered expression of these cytokines or their receptors and analyses of mutations and polymorphisms in human genes that encode these products have provided important information about IL and IFN functions. We discuss their signaling pathways, cellular sources, targets, roles in immune regulation and cellular networks, roles in allergy and asthma, and roles in defense against infections. (J Allergy Clin Immunol 2011;127:701-21.)

Key words: *Cytokines, interleukins, T cells, B cells, dendritic cells, adaptive immune response, humoral immune response, allergy and asthma*

Abbreviations used

APC:	Antigen-presenting cell
CSF:	Colony-stimulating factor
DC:	Dendritic cell
FoxP3:	Forkhead box protein 3
γc:	γ-Chain
G-CSF:	Granulocyte colony stimulation factor
IBD:	Inflammatory bowel disease
IL-1F:	IL-1 family
IL-1RI:	IL-1 type I receptor
IL-1RII:	IL-1 type II receptor
IL-1Ra:	IL-1 receptor antagonist
IL-1RacP:	IL-1 receptor accessory protein
MS:	Multiple sclerosis
NK:	Natural killer
NKT:	Natural killer T
Poly I:C:	Polyriboinosinic:polyribocytidylic acid
R:	Receptor
RA:	Rheumatoid arthritis
Tbet:	T-box expressed in T cells
TLR:	Toll-like receptor
Tr1:	Type 1 regulator T
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

Since the discovery of IL-1 in 1977, approximately 200,000 published articles have referred to ILs. Secreted proteins that bind to their specific receptors and play a role in the communication among leukocytes are named ILs. The nomenclature is continuously evolving, and there have been proposals for the assignment of new members to the IL-1 family.[1] ILs are assigned to each family based on sequence homology and receptor chain similarities or functional properties (Fig 1). $CD4^+$ T_H cells are divided into distinct subsets according to cytokine profile. The profile of cytokine expression depends on the adjuvanicity of the molecules presented with the antigen and the status of the T cells, along the types of antigen-presenting cells (APCs) and cytokines in the microenvironment. $CD4^+$ naive T cells can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, and T-follicular effector cells. On the basis of their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can promote different types of inflammatory responses (Fig 2). During the development of allergic disease, effector T_H2 cells produce IL-4, IL-5, IL-9, and IL-13[2,3]; their production of IL-25, IL-31, and IL-33 contributes to T_H2 responses and inflammation.[4-7] These cytokines have roles in production of allergen-specific IgE, eosinophilia, and mucus. T_H1 cells, however, produce the cytokine IFN-γ, which protects against intracellular pathogens and plays a role in activation-induced death of skin keratinocytes, mucosal epithelial cells, and T cells.[8,9]

From the Swiss Institute of Allergy and Asthma Research, University of Zurich.

The authors' laboratories are supported by Swiss National Foundation grants and the Christine Kühne Center for Allergy Research and Education.

Disclosure of potential conflict of interest: M. Akdis has received research support from the Swiss National Foundation and Imvision GmbH. L. O'Mahony has collaborated with Alimentary Health Ltd and has received research support from the Swiss National Science Foundation. C. A. Akdis has received research support from Novartis, Stallergenes, the Swiss National Science Foundation, the Global Allergy and Asthma European Network, and the Christine Kühne Center for Allergy Research and has consulted for Actellion, Aventis, and Allergopharma. The rest of the authors have declared that they have no conflict of interest.

Received for publication August 19, 2010; revised November 11, 2010; accepted for publication November 12, 2010.

Reprint requests: Cezmi A. Akdis, MD, Swiss Institute of Allergy and Asthma Research, Obere Strasse 22, CH7270 Davos, Switzerland. E-mail: akdisac@siaf.uzh.ch.

0091-6749/$36.00

doi:10.1016/j.jaci.2010.11.050

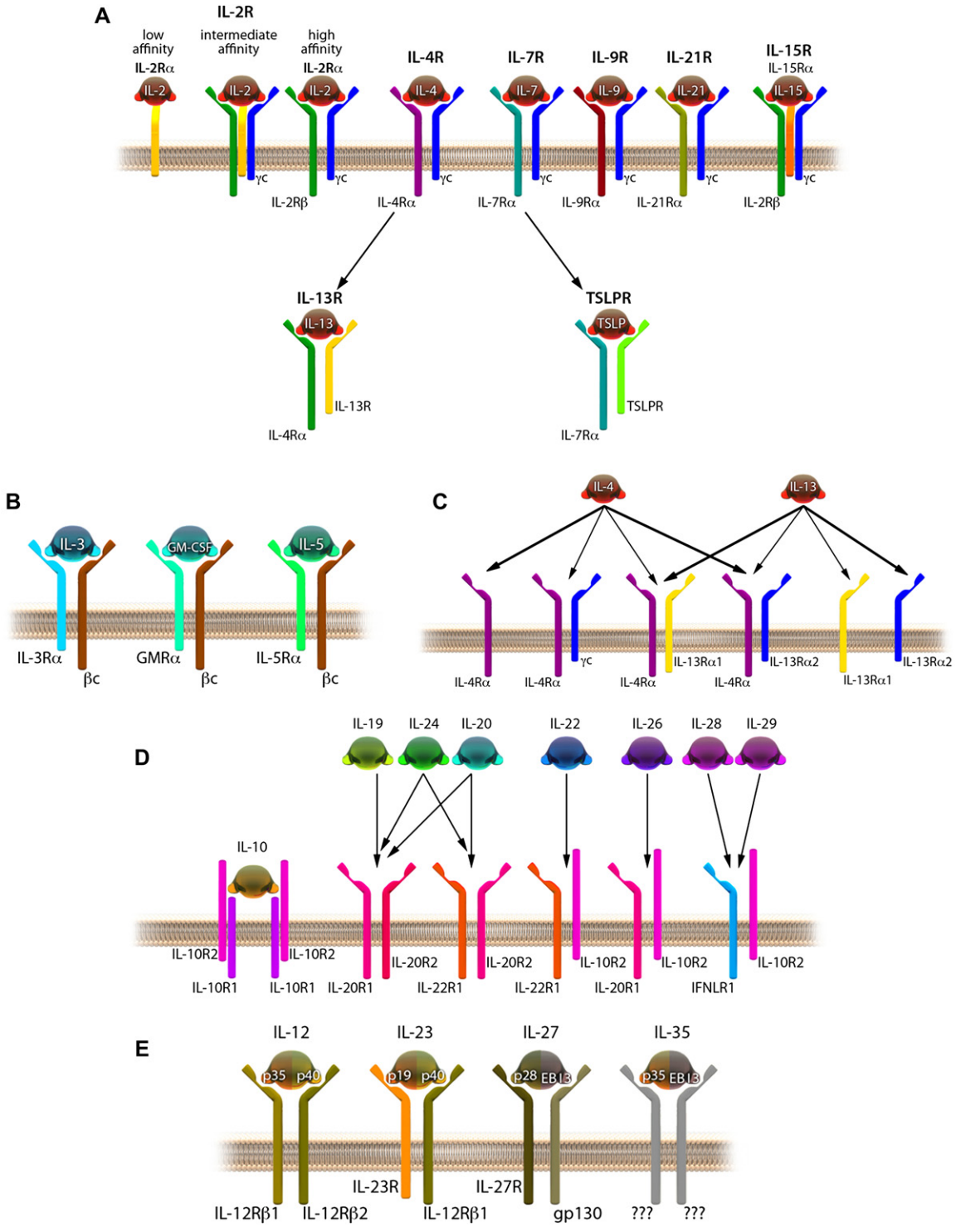

FIG 1. A, The receptors of the IL-2 family, which is composed of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Receptors contain the common cytokine receptor γ chain (CD132, γc). IL-13R shares IL-4Rα with IL-4, and TSLPR shares IL-7R with IL-7. **B,** The receptors for IL-3, IL-5, and GM-CSF *(GMR)* are heterodimers of a unique α-chain and the common β-chain (βc, CD131) subunit. **C,** The receptors for IL-4 and IL-13 consists of 2 receptor chains, the IL-4Rα (CD124) and the common γc. IL-4 and IL-13 bind to IL-4R, which consists of the IL-4Rα and the IL-13Rα1 chain. IL-13R consists of 2 subunits, IL-13Rα1 and IL-13Rα2, and signaling occurs via the IL-4R complex type II that consists of the IL-4Rα and IL-13Rα. **D,** On the basis of similarities in their intron-exon structure, conserved secondary protein structures, and similar types of receptors, the following cytokines have been classified as IL-10 family members: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29. They share common receptor subunits shown. **E,** IL-12R consist of 2 subunits, IL-12Rβ1 and IL-12Rβ2.A heterodimer of IL-12Rβ1 and IL-23R bind IL-23. IL-12Rβ2 shows homology to the gp130 subunit of IL-27R. *EBI3*, Epstein-Barr virus-induced.