

THE JOURNAL OF Allergy AND Clinical Immunology

January 1997 • Volume 99 • Number 1

Interleukin-4 and its receptor: Essential mediators of the allergic response

John J. Ryan, PhD [[MEDLINE
LOOKUP](#)]

- *Bethesda, Md.*

Sections

- [IL-4: Structure, Function, and Control of Expression](#)
- [IL-4 Receptor: Structure and Signal Transduction](#)
- [Role of IL-4 in Health and Disease: a Synthesis](#)
- [Future Directions](#)
- [References](#)
- [Publishing and Reprint Information](#)
- [Articles with References to this Article](#)

- [Next article](#) in Issue
- [Drug links](#) from Mosby's DrugConsult
- [Genetic information](#) from OMIM
- Citation of this Article
 - View on [PubMed](#)
 - Download in [citation manager format](#)
 - Download in [Medlars format](#)
- [Related articles](#) in PubMed

IL-4R Interleukin-4 receptor

JAK Janus family kinase

STAT Signal transducer and activator of transcription

Allergic diseases including allergic rhinitis, urticaria, conjunctivitis, food allergies, asthma, and

systemic anaphylaxis affect approximately one fourth of the American population. Atopic responses cause considerable mortality; nearly 5000 deaths were caused by asthma in 1992. Importantly, the incidence and death rate of asthma have increased in recent years, with a tripling of hospital discharges from 1970 to 1987 and a 31% increase in deaths from 1980 to 1987.¹

IL-4 is essential in the development of allergic diseases because of its influence over helper T cell (TH) development and the production of IgE. Of the many T-cell–derived cytokines, IL-4 alone has been shown to have such a singular impact, directing the host response toward humoral immunity and away from cell-mediated protection. This critical role of IL-4 is examined in this review with focuses on IL-4 and IL-4 receptor (IL-4R) structure, expression, and role in clinical disease.

IL-4: Structure, Function, and Control of Expression

[TOP](#)

Human IL-4 is an 18 to 20 kd glycoprotein composed of 153 amino acids with 50% homology to mouse IL-4. Both cytokines act in a species-specific manner. IL-4 is produced by T cells, mast cells, and basophils in response to cross-linkage of the T-cell antigen receptor or high-affinity IgE receptors on mast cells and basophils. Production is rapid and transient, with detectable IL-4 made in 1 to 5 hours and loss of expression after 24 to 48 hours.

IL-4 exerts pleiotropic effects,² which together emphasize a humoral response. Arguably the most important effect of IL-4 is its role in T-cell development. As shown in detail with mouse studies, TH cells can be delineated into two subsets: those that produce IL-2, interferon- γ , tumor necrosis factor- β and enhance cell-mediated immunity (TH1 cells) and those that produce IL-4, IL-5, IL-6, IL-10, and IL-13 and drive the humoral response, including the production of IgE (TH2 cells). IL-4 directs the development of the TH2 lineage. Moreover, mouse studies have demonstrated a dominant role for IL-4 in TH1/TH2 development. Although IL-12 enhances TH1 differentiation, IL-4 can overcome IL-12 stimulation under some conditions. IL-4 is also known to be important for in vivo TH2 development, because mice bearing germline mutations in the IL-4 gene show impaired TH2 responses.

IL-4 directs B-cell production of IgE and IgG₄, while co-stimulating proliferation, and also directs the upregulation of CD23, Class II major histocompatibility antigens, IL-4R, CD40, IL-2R β , and Thy-1. This production of IgE is central to the development of atopic diseases. Patients with allergy mount an IgE response to most antigens, a response that directly correlates with the development of TH cells producing IL-4 and related cytokines.

Macrophages show increased CD23 expression, antigen-presenting abilities, and tumor killing in response to IL-4; however, macrophage-mediated inflammatory responses are inhibited, with decreased production of IL-1, IL-6, IL-8, tumor necrosis factor, H₂O₂, nitric oxide, and prostaglandin E₂. Endothelial cells respond to IL-4 with an upregulation of the adhesion molecule, vascular cell adhesion molecule-1, while decreasing expression of intercellular adhesion molecule-1 and endothelial adhesion molecule-1. This has been postulated to lead to a selective egress of eosinophils from the circulatory system to cutaneous areas of inflammation, an activity that is enhanced by mast cell–derived mediators. IL-4 is also a co-factor for mast cell growth. Major characteristics and activities of IL-4 are summarized in Table I.

Table I. IL-4 and IL-4 R: Characteristics and activities

Protein	Size	Expression
IL-4	18-20 kd	T cells, mast cells, basophils
IL-4R	145 kd	Widely expressed including: T, B, mast, endothelial cells, and macrophages
Cell type	IL-4–stimulated activities	
T cell	TH ₂ development leading to production of IL-4, 5, 6, 10, 13	
B cell	Production of IgE and IgG ₄ ; upregulation of CD23, Class II MHC Ag, IL-4R, CD40, IL-2Rβ, Thy-1	
Macrophage	Increased CD23, Ag presentation, tumor killing; decreased production of IL-1, IL-6, IL-8, TNF, H ₂ O ₂ , PGE ₂	
Endothelial	Increased expression of VCAM-1; decreased expression of ICAM-1 and ELAM-1	
<i>MHC</i> , Major histocompatibility complex; <i>Ag</i> , antigen; <i>TNF</i> , tumor necrosis factor; <i>PGE₂</i> , prostaglandin E ₂ ; <i>VACM-1</i> , vascular cell adhesion molecule-1; <i>ICAM-1</i> , intracellular adhesion molecule-1; <i>ELAM-1</i> , endothelial adhesion molecule-1.		

The gene for IL-4 is found in a cluster of cytokine genes on human chromosome 5q23-31 including the genes for IL-3, IL-4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor, all of which are produced by T_{H2} cells and most of which are found in the allergic response.

A key event in the control of IL-4 production is the initial production of IL-4, which is needed to drive the T_{H2} response, which then maintains IL-4 levels. A population of NK1.1⁺, CD4⁺ T cells has been shown to rapidly produce IL-4 after in vivo treatment with anti-CD3 antibodies.³ This population may provide sufficient IL-4 to initiate T_{H2} development. Also, a T_{H2} transcription factor termed *c-maf* has recently been shown to be capable of directing transcription from an IL-4 promoter/ reporter construct in lymphoid and nonlymphoid cell lines.³ These advances have begun to explain important aspects of IL-4 regulation.

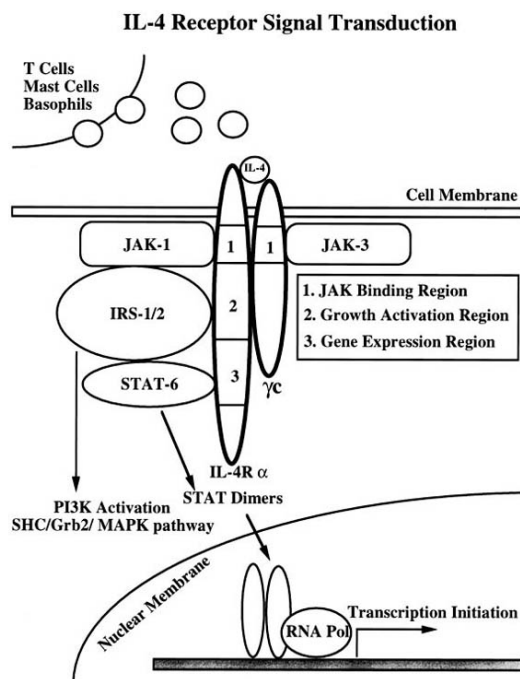
IL-4 Receptor: Structure and Signal Transduction

TOP

Human IL-4R is found on T cells, B cells, mast cells, basophils, macrophages, fibroblasts, endothelial cells, hepatocytes, keratinocytes, stromal cells, and neuroblasts. A large integral membrane glycoprotein, IL-4R is composed of 825 amino acids, of which 560 are intracellular. IL-4R bears characteristics similar to those of other Type I hematopoietin receptors with two fibronectin type III domains, four paired cysteines, and the conserved WSXWS motif in its extracellular region. IL-4R forms a complex with the protein now denoted as γ_c , which is also known to function as part of the receptors for IL-2, IL-7, IL-9, and IL-15. Neither IL-4R nor γ_c has any known endogenous kinase activities.

Signal transduction through IL-4R uses multiple domains of the intracellular region to induce proliferative and gene expression responses (Fig. 1).

Fig. 1. Model of IL-4 receptor signal transduction. IL-4 produced by TH2 cells, mast cells, or basophils binds to the IL-4R complex, composed of IL-4R α and γ_c . The IL-4R uses multiple intracellular domains for binding of Janus family kinases and for binding and activation of IRS-1, IRS-2, and STAT-6 proteins through tyrosine phosphorylation. IRS-1 and IRS-2 link the IL-4R to downstream signaling cascades, leading to cell growth. STAT protein phosphorylation is believed to induce transcriptional activation after the STAT dimers translocate from the receptor to the nucleus, where they bind to specific promoter elements. *PI3K*, phosphoinositol 3' kinase; *SHC*, SH2-domain, collagen-homology protein; *Grb2*, growth factor receptor-bound protein-2. *MAPK*, mitogen-activated kinase.



[Click on Image to view full size](#)

The membrane proximal region of the receptor contains sequences known as Box 1 and Box 2, which have been found to bind the Janus family tyrosine kinases JAK-1 (bound to IL-4R) and JAK-3 (bound to γ_c). Distal to this region is the IL-4R motif, a region of sequence homology found in the insulin, insulin-like growth factor-1, and IL-4 receptors. This motif and its central tyrosine are essential for the tyrosine phosphorylation of Insulin Receptor Substrates-1 and -2 (IRS-1, IRS-2)

and adaptor proteins responsible for growth activities of the receptor by linking the receptor to various downstream signaling pathways, including phosphoinositol 3' kinase and mitogen-activated kinase. A more distal region of the receptor, termed *the gene expression domain*, contains three tyrosine residues, which mediate activation of the signal transducer and activator of transcription (STAT)-6 and related gene expression. Thus the IL-4R, like many of the hematopoietin receptors, uses the JAK-STAT pathway for transcriptional control, although the exact mechanism of this control is unknown. For further details on IL-4 signal transduction, see the articles by Keegan et al.⁵ and Ryan et al.⁶

Role of IL-4 in Health and Disease: a Synthesis

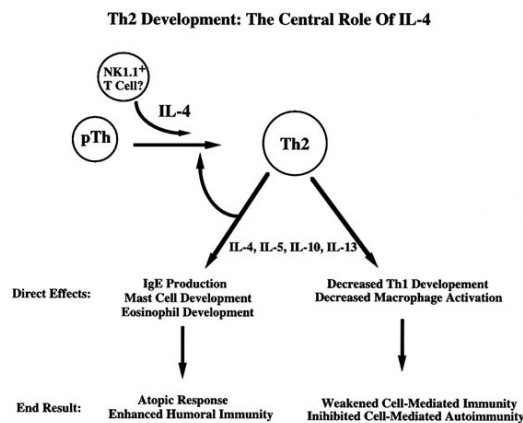
[TOP](#)

Understanding IL-4 production and signal transduction offers treatment possibilities for many diseases. Not only is IL-4 production central to allergic reactions, but animal studies have also shown IL-4 to be the deciding factor in responses to various pathogens. Mice mounting an IL-4–dominated response to the intracellular protozoan *Leishmania major* succumb to infection, whereas those with an interferon- γ –dominated response survive. Blocking the IL-4 response allows susceptible mice to survive, whereas IL-4 treatment of resistant mice renders them susceptible. Alternatively, IL-4 has been shown to be essential for resistance to the extracellular pathogens *Heligomosoides polygyrus* and *Trichiuris muris*. For a review of the role of cytokines in infection, see the article by Paul and Seder.⁷

IL-4 has also been shown to have antitumor effects. In addition to directly inhibiting the growth of some colon carcinomas, transfection of the IL-4 gene induced in vivo killing of many tumor types.⁸ These studies demonstrated an important role for IL-4 in eosinophil infiltration, with subsequent tumor cell killing. These indirect effects are of potentially great importance, because they are effective against many tumor types and help to explain some of the pathology concomitant with allergic diseases, which often involve eosinophil infiltration.

As shown in Fig. 2, IL-4 can be viewed as a dual player in the immune system.

Fig. 2. Summary of TH2 development and central role of IL-4. IL-4 is initially provided by an unknown source, possibly NK1.1⁺ cells, during the immune response. The presence of IL-4 during development from a precursor T helper cell (*pTh*) leads to formation of TH2 cells. Cytokine secretion by TH2 cells has the net effect of increasing humoral immunity, with concomitant induction of allergic responses, while decreasing cellular immunity.



While driving allergic disease induction, it also offers protection from extracellular infections and cell-mediated tissue destruction. After the initiation of the TH2 response, IL-4 and IL-10 hamper TH1 and macrophage activity with the net effects of decreased cellular immunity, weakened protection from intracellular pathogens, and a possible inhibition of the cell-mediated damage found in some autoimmune diseases. The TH2 cytokines IL-3, IL-4, IL-5, and IL-13 promote antibody formation, mast cell development, and eosinophil migration to sites of inflammation. Thus allergic disease and humoral autoimmunity are manifested, and protection from extracellular infections is promoted.

Future Directions

[TOP](#)

In addition to providing possible therapies for clinical states directly related to IL-4, an understanding of this receptor signaling pathway could offer insight into other cytokine pathways related to allergic disease, infection, autoimmunity, and cancer. Several essential areas of research are described below.

Regulation of IL-4 production

Although the description of IL-4-producing NK1.1⁺ T cells and the demonstration of c-maf's role in IL-4 production have furthered our knowledge, TH2 development remains unclear. A human equivalent for NK1.1⁺ T cells may have recently been found. The functional role of these cells needs to be elucidated. Also, an understanding of IL-4 deregulation in patients with hereditary atopy is essential. In concert with these studies is a basic understanding of IL-4R signaling, which drives TH2 development.

Shifting of established Th phenotypes

Understanding cytokine signaling will only be useful if this knowledge can be used in established disease. Recently, data from mouse models have indicated that established TH1 or TH2 cells can be shifted to the alternative phenotype under appropriate conditions. These experiments need to be reproduced in the human system and evaluated for possible clinical use.

Creation of IL-4/IL-13 antagonists

Although IL-4 has been shown to be a key player in atopy, IL-13 can mimic many of these effects, with the notable exception of TH2 differentiation. Therefore cytokine-mediated inhibition of the allergic response will depend on blocking both IL-4 and IL-13 activities. One such inhibitor has been derived, a mutated form of human IL-4 termed *Y124D*. Therapeutic usefulness of this inhibitor awaits clinical trials. Important to these studies is the derivation of a murine homolog to Y124D for use in the many animal model systems already in existence.

Control of TH differentiation for vaccine development

If the initiation of IL-4 production can be controlled, so too can the choice of TH cell responses. This would allow for the development of vaccines to pathogens or established tumors, which could select for the appropriate TH response, greatly increasing vaccine efficacy. Success in this area depends on a more basic understanding of IL-4 expression and signal transduction.

I thank William E. Paul, Hua Huang, Nancy Noben-Traut, and Claudia Ryan for thoughtful review of this manuscript.

References

TOP

1. Ellis E. Asthma. In: Berkow R, editor. Merck manual of diagnosis and therapy. 16th ed. Merck Research Laboratories, 1992:646.

2. Paul WE, Ohara J. B cell stimulatory factor-1/interleukin-4. Annu Rev Immunol 1987;5:429-59.

MEDLINE

3. Yoshimoto T, Bendelac A, Watson C, Hu-Li J, Paul WE. Role of NK1.1 T cells in a Th2 response and in immunoglobulin E production. Science 1995;270:1845-7.

MEDLINE

4. Ho I-C, Hodge M, Rooney J, Glimcher L. The proto-oncogene c-maf is responsible for tissue-specific expression of interleukin-4. Cell 1996;85:973-83.

MEDLINE

5. Keegan A, Nelms K, Wang L-M, Pierce J, Paul WE. Interleukin-4 receptor: signaling mechanisms. Immunol Today 1994;15:423-32.

MEDLINE

6. Ryan J, McReynolds L, Keegan A, Wang L-H, Garfein E, Rothman P, et al. Growth and gene expression are predominantly controlled by distinct regions of the human IL-4 receptor. Immunity 1996;4:123-32.

MEDLINE

7. Paul WE, Seder R. Lymphocyte responses and cytokines. *Cell* 1994;76:241-51.

MEDLINE

8. Tepper R. The anti-tumor and proinflammatory actions of IL4. *Res Immunol* 1994;144:633-6.

Publishing and Reprint Information

TOP

- *From Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda.*
- *The author is supported by a Cancer Research Institute/Miriam and Benedict Wolf Fellowship.*
- *Received for publication Oct. 4, 1996.*
- *Accepted for publication Oct. 11, 1996.*
- *Reprint requests: John J. Ryan, PhD, NIH/NIAID, Laboratory of Immunology, Building 10, Room 11N311, Bethesda, MD 20892.*
- *J Allergy Clin Immunol 1997;99:1-5.*
- **1/1/78546**
- *Copyright © 1997 by Mosby–Year Book, Inc.*

Articles with References to this Article

TOP

This article is referenced by these articles:

***Fusarium culmorum* causes strong degradation of pollen allergens in extract mixtures**

Journal of Allergy and Clinical Immunology, The

January 2002, part 1 • Volume 109 • Number 1

Michael Hoff, MSc, Marion Krail, Marion Kästner, Dieter Haustein, PhD, Stefan Vieths, PhD

ABSTRACT

FULL TEXT

Biologic pollution in infant bedding in New Zealand: High allergen exposure during a vulnerable period

Journal of Allergy and Clinical Immunology, The

November 1998 • Volume 102 • Number 5

Gill Sawyer, RGN, Trudi Kemp, MRCP, Robyn Shaw, FRACP, Kathryn Patchett, MB, ChB, Robert Siebers, FNZIMLS, Simon Lewis, BSc, Richard Beasley, MD, Julian Crane, FRACP, Penny Fitzharris, MD

ABSTRACT

FULL TEXT