

# Interleukin-4 (IL-4) and IL-13 bind to a shared heterodimeric complex on endothelial cells mediating vascular cell adhesion molecule-1 induction in the absence of the common gamma chain

B Schnyder, S Lugli, N Feng, H Etter, RA Lutz, B Ryffel, K Sugamura, H Wunderli- Allenspach and R Moser

Department of Pharmacy, Biopharmacy, Federal Institute of Technology, Zurich, Switzerland.

Interleukin-4 (IL-4) and IL-13 exert similar, nonadditive effects on endothelial cells, inducing vascular cell adhesion molecule-1 (VCAM-1) expression and subsequent transmigration of eosinophils. The receptor for IL-4 and IL-13 was described as a shared heteromultimeric complex in which the common gamma-chain (gamma c) subunit was essential for activity. Endothelial cell bound both cytokines with high affinity; by flowcytometry and reverse transcription-polymerase chain reaction (RT-PCR), they expressed IL-4 receptor alpha (IL-4R alpha) but did not express the gamma c of the IL-2R. Radioligand cross-linking experiments followed by immunoprecipitation with the monoclonal antibody (MoAb) S697 to the IL-4R alpha showed IL-4-specific binding at 130 kD, the IL-4R alpha, and to a minor extent to a double band coimmunoprecipitated at 65 to 75 kD. [125 I]IL-13 bound predominantly to the 65- to 75- kD band and with a trace amount of binding at 130 kD. However, no ligand-cross-linked receptor was precipitated by the MoAb S697, indicating a cognate novel IL-13-binding subunit. Excess unlabeled IL-4 completely displaced IL-13 binding. Similarly, nonsignaling IL-4 (Y124D)-mutant abolished IL-4- and IL-13-mediated signal transduction. Unlabeled IL-13 competed successfully for IL-4 binding at 65 to 75 kD but was unable to completely displace IL-4 from its binding to the IL-4R alpha. The MoAb TUGh4, specific for the gamma c, failed to precipitate ligand-cross-linked IL-4R and IL-13R. Therefore, the subunit structure of the functional receptors for IL-4 and IL-13 on human endothelial cells does not use or require the common gamma c of the IL-2R.

Volume 87, Issue 10, pp. 4286-4295, 05/15/1996

Copyright © 1996 by The American Society of Hematology

## This article has been cited by other articles:

- Taylor, N., Candotti, F., Smith, S., Oakes, S. A., Jahn, T., Isakov, J., Puck, J. M., O'Shea, J. J., Weinberg, K., Johnston, J. A. (1997). Interleukin-4 Signaling in B Lymphocytes from Patients with X-linked Severe Combined Immunodeficiency. *J. Biol. Chem.* 272: 7314-7319 [[Abstract](#)] [[Full Text](#)]
- Candotti, F., Oakes, S. A., Johnston, J. A., Giliani, S., Schumacher, R. F., Mella, P., Fiorini, M., Ugazio, A. G., Badolato, R., Notarangelo, L. D., Bozzi, F., Macchi, P., Strina, D., Vezzoni, P., Blaese, R. M., O'Shea, J. J., Villa, A. (1997). Structural and Functional Basis for JAK3-Deficient Severe Combined Immunodeficiency. *Blood* 90: 3996-4003 [[Abstract](#)] [[Full Text](#)]
- Blease, K., Seybold, J., Adcock, I. M., Hellewell, P. G., Burke-Gaffney, A. (1998). Interleukin-4 and Lipopolysaccharide Synergize to Induce Vascular Cell Adhesion Molecule-1 Expression in Human Lung Microvascular Endothelial Cells. *Am J Respir Cell Mol Biol* 18: 620-630 [[Abstract](#)] [[Full Text](#)]
- Volpert, O. V., Fong, T., Koch, A. E., Peterson, J. D., Waltenbaugh, C., Tepper, R. I., Bouck, N. P. (1998). Inhibition of Angiogenesis by Interleukin 4. *J. Exp. Med.* 188: 1039-1046 [[Abstract](#)] [[Full Text](#)]
- Georas, S. N., Cumberland, J. E., Burke, T. F., Chen, R., Schindler, U., Casolaro, V. (1998). Stat6 Inhibits Human Interleukin-4 Promoter Activity in T Cells. *Blood* 92: 4529-4538 [[Abstract](#)] [[Full Text](#)]
- Jayawickreme, S. P., Gray, T., Nettesheim, P., Eling, T. (1999). Regulation of 15-lipoxygenase expression and mucus secretion by IL-4 in human bronchial epithelial cells. *Am. J. Physiol.* 276: 596L-603 [[Abstract](#)] [[Full Text](#)]
- NOGUCHI, E., SHIBASAKI, M., ARINAMI, T., TAKEDA, K., YOKOUCHI, Y., KOBAYASHI, K., IMOTO, N., NAKAHARA, S., MATSUI, A., HAMAGUCHI, H. (1999). No Association between Atopy/Asthma and the Ile50val Polymorphism of IL-4 Receptor. *Am J Respir Crit Care Med* 160: 342-345 [[Abstract](#)] [[Full Text](#)]
- Pesu, M., Takaluoma, K., Aittomäki, S., Lagerstedt, A., Saksela, K., Kovanen, P. E., Silvennoinen, O. (2000). Interleukin-4-induced transcriptional activation by Stat6 involves multiple serine/threonine kinase pathways and serine phosphorylation of Stat6. *Blood* 95: 494-502 [[Abstract](#)] [[Full Text](#)]
- Suzuki, K., Nakajima, H., Watanabe, N., Kagami, S.-i., Suto, A., Saito, Y., Saito, T., Iwamoto, I. (2000). Role of common cytokine receptor gamma chain (gamma c)- and Jak3-dependent signaling in the proliferation and survival of murine mast cells. *Blood* 96: 2172-2180 [[Abstract](#)] [[Full Text](#)]

- Grunewald, S. M., Werthmann, A., Schnarr, B., Klein, C. E., Brocker, E. B., Mohrs, M., Brombacher, F., Sebald, W., Duschl, A. (1998). An Antagonistic IL-4 Mutant Prevents Type I Allergy in the Mouse: Inhibition of the IL-4/IL-13 Receptor System Completely Abrogates Humoral Immune Response to Allergen and Development of Allergic Symptoms In Vivo. *The JI* 160: 4004-4009 [\[Abstract\]](#) [\[Full Text\]](#)
- Guillot, C., Coathalem, H., Chetritt, J., David, A., Lowenstein, P., Gilbert, E., Tesson, L., van Rooijen, N., Cuturi, M. C., Soullilou, J.-P., Anegon, I. (2001). Lethal Hepatitis After Gene Transfer of IL-4 in the Liver Is Independent of Immune Responses and Dependent on Apoptosis of Hepatocytes: A Rodent Model of IL-4-Induced Hepatitis. *The JI* 166: 5225-5235 [\[Abstract\]](#) [\[Full Text\]](#)
- Bonder, C. S., Dickensheets, H. L., Finlay-Jones, J. J., Donnelly, R. P., Hart, P. H. (1998). Involvement of the IL-2 Receptor  $\gamma$ -Chain ( $\gamma$ c) in the Control by IL-4 of Human Monocyte and Macrophage Proinflammatory Mediator Production. *The JI* 160: 4048-4056 [\[Abstract\]](#) [\[Full Text\]](#)
- Introna, M., Mantovani, A. (1997). Early Activation Signals in Endothelial Cells: Stimulation by Cytokines. *Arterioscler Thromb* 17: 423-428 [\[Abstract\]](#) [\[Full Text\]](#)
- Ford, D., Sheehan, C., Girasole, C., Priester, R., Kouttab, N., Tigges, J., King, T. C., Luciani, A., Morgan, J. W., Maizel, A. L. (1999). The Human B Cell Response to IL-13 Is Dependent on Cellular Phenotype as Well as Mode of Activation. *The JI* 163: 3185-3193 [\[Abstract\]](#) [\[Full Text\]](#)
- Shanafelt, A. B., Forte, C. P., Kasper, J. J., Sanchez-Pescador, L., Wetzel, M., Gundel, R., Greve, J. M. (1998). An immune cell-selective interleukin 4 agonist. *Proc. Natl. Acad. Sci. U. S. A.* 95: 9454-9458 [\[Abstract\]](#) [\[Full Text\]](#)
- Thompson, J. P., Debinski, W. (1999). Mutants of Interleukin 13 with Altered Reactivity toward Interleukin 13 Receptors. *J. Biol. Chem.* 274: 29944-29950 [\[Abstract\]](#) [\[Full Text\]](#)
- Lugli, S. M., Feng, N., Heim, M. H., Adam, M., Schnyder, B., Etter, H., Yamage, M., Eugster, H.-P., Lutz, R. A., Zurawski, G., Moser, R. (1997). Tumor Necrosis Factor alpha Enhances the Expression of the Interleukin (IL)-4 Receptor alpha -Chain on Endothelial Cells Increasing IL-4 or IL-13-induced Stat6 Activation. *J. Biol. Chem.* 272: 5487-5494 [\[Abstract\]](#) [\[Full Text\]](#)