The EMBO Journal vol.13 no.6 pp.1350 – 1356, 1994

STF – IL-4: a novel IL-4-induced signal transducing factor

Chris Schindler[1], Helena Kashleva[1], Alessandra Pernis[1], Richard Pine[3] and Paul Rothman[1,2,4]

[1]Department of Medicine and [2]Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York, NY 10032 and [3]Public Health Resource Institute and Department of Microbiology, New York University Medical Center, New York, NY 10016, USA
[4]Corresponding author

Communicated by B.Pernis

The mechanism by which interleukin-4 (IL-4) regulates the expression of particular genes is unknown. We have determined that IL-4 induces a DNA binding factor (termed STF – IL-4) which has a strong affinity for an IFN-γ activation site (GAS). Interestingly, STF – IL-4 also binds to the IL-4 responsive promoter for the Ig heavy chain germline ε transcript. The IL-4 dependent activation of STF – IL-4 is rapid, does not require protein synthesis and results in the sequential appearance of binding activity first in the cytoplasm and then later in the nucleus. Activation of STF – IL-4 is sensitive to tyrosine kinase inhibitors and the active factor is tyrosine phosphorylated. This pattern of activation is similar to the activation of interferon-induced transcription factors. STF – IL-4 appears to be a new member of a growing family of cytokine-induced transcriptional regulators.

Key words: cytokine/interferon/interleukin-4/signal transduction

Introduction

Interleukin-4 (IL-4), which is produced by T cells, mast cells and basophils, has potent biological activities on many different cells, including B and T lymphocytes, mast cells and macrophages (reviewed in Spits, 1992). When cells are cultured with IL-4, it often stimulates a variety of different functions within a given cell type. For instance, IL-4 can stimulate B cells to proliferate and differentiate (reviewed in Paul and Ohara, 1987), alter the level of cell surface receptors such as MHC class II (Noelle *et al.*, 1984; Roehm *et al.*, 1984) and CD23 (Defrance *et al.*, 1987; Hudak *et al.*, 1987), and stimulate the B cells to undergo Ig heavy chain class-switching to IgG1 and IgE (reviewed in Coffman *et al.*, 1993). Many of these biological activities rely on IL-4's ability to stimulate the transcription of particular genes. For instance, the ability of IL-4 to stimulate Ig heavy chain class-switching to IgG1 and IgE is dependent on its ability to stimulate germline γ1 and ε transcription prior to switching (reviewed in Coffman *et al.*, 1993).

The gene encoding the IL-4 cellular receptor has been cloned (reviewed in Izuhara *et al.*, 1993) and is a member of the hematopoietin receptor superfamily (Cosman, 1993). The gene encodes a 140 000 kDa molecule which contains a conserved pattern of cysteine residues as well as a WSXWS box, which are found in other members of this superfamily of cell surface receptors (Miyajima *et al.*, 1992). In addition, the IL-4 receptor does not contain recognizable kinase domains. Although the ability of IL-4 to induce the transcription of certain genes has been well documented, the mechanism by which the binding of IL-4 to its receptor stimulates transcription of these genes remains unknown. Murine IL-4 does not seem to activate a cell through the mobilization of Ca^{2+} or by activation of the phosphoinositol pathway (Justement *et al.*, 1986; Mizuguchi *et al.*, 1986).

Recently, the pathway by which the interferons (IFNs) stimulate transcription of early response genes has been elucidated (reviewed in Pellegrini and Schindler, 1993). The binding of IFN (either α/β or γ) to its receptor stimulates the activation by tyrosine phosphorylation, of latent cytoplasmic transcription factors, termed signal transducing factors (STF) – IFN-α/β or – IFN-γ, respectively. After this phosphorylation event, these factors translocate to the nucleus where, after binding to specific DNA elements [ISRE and the IFN-γ activation site (GAS) respectively] in the promoter of responsive genes, they function as transcriptional activators. The components of these STF complexes have been purified and cloned, and appear to represent a novel class of transcriptional activators. One of these proteins, p91, is a component of both STF – IFN-α and STF – IFN-γ (reviewed in Pellegrini and Schindler, 1993).

This system of signal transduction is important in the biological response to IFNs which require the rapid activation of specific target genes. It appears that other cytokines may employ a related signaling paradigm. For instance, both CNTF (Bonni *et al.*, 1993) and EGF (Sadowski *et al.*, 1993) rapidly activate STFs after binding to their respective receptors. Interestingly, the p91 protein appears to be a component of both STF – CNTF and STF – EGF (Bonni *et al.*, 1993; Silvennoinen *et al.*, 1993a,b). Recent evidence indicates that other cytokines also induce STFs and that several of these STFs bind to a site in the promoter of the *IRF-1* (ISGF2) gene (termed IRF-1 GAS) which has been shown to bind STF – IFN-γ (Pine *et al.*, 1994; P.Rothman and C.Schindler, unpublished observations).

IL-4 and IFN-γ are produced by different subsets of $CD4^+$ helper T cells (reviewed in Mosmann and Coffman, 1989). These two cytokines regulate several steps in B cell development. One model by which two different cytokines could regulate the transcription of the same genes would involve similar pathways of signal transduction. In an effort to characterize a putative STF that could mediate the effects of IL-4 on B cell development, we determined that IL-4 rapidly activates a novel STF which has an affinity for the GAS element. The activation and activity of this factor (termed STF – IL-4) share many biological features with the IFN pathway. In addition, STF – IL-4 binds to a sequence at the IL-4 inducible promoter of the Ig germline ε transcript that differs significantly from the GAS element.