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Molecules in Focus

# Interleukin-1

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**Abstract**

Interleukin 1 (IL1) is a primary regulator of inflammatory and immune responses. Via its type I receptor it activates specific protein kinases, including the NFκB inducing kinase (NIK) and three distinct mitogen-activated protein (MAP) kinase cascades. These modulate a number of transcription factors including NFκB, AP1 and CREB each of which regulate a plethora of immediate early genes central to the inflammatory response. Phase I clinical trials of the soluble type I receptor and IRAP indicate that these have potential anti-inflammatory effects. 

*Keywords:* Interleukin 1; MAP kinases; Signalling; NFκB

## 1. Introduction

IL1 was originally purified under a number of names corresponding to its different biological activities (endogenous pyrogen, lymphocyte activating factor, thymocyte proliferation factor, catabolin, amongst others). It was given the unifying term interleukin 1 in 1979.

## 2. Structure and function

Three members of the IL1 family have been cloned [1]. All bind both types of receptor (see below) but only two IL1α and IL1β, (encoded on chromosome 2) are agonistic. The third is the interleukin 1 receptor antagonist protein (IRAP). All share 20–25% amino acid homology. Mature IL1α and β have similar three-dimensional open barrel structures of β sheets.

## 3. Synthesis and degradation

IL1 α and β are made mainly by monocytes and macrophages, but also by endothelial cells, fibroblasts and epidermal cells. They are produced in response to many stimuli including bacterial lipopolysaccaride (LPS), other microbial products, cytokines (TNF, interferon γ, GM-CSF, IL2), T cell/antigen presenting cell interactions and immune complexes. IRAP is also made by monocytes and a variety of other cell

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types. IL1 α and β are synthesised as cytosolic precursors (31 kD) which are cleaved to generate the mature proteins (17 kD) [1] and released by unknown mechanisms. ProIL1β is cleaved by the cysteine proteinase interleukin 1β converting enzyme (ICE). There are two transcripts of IRAP: the secreted glycosylated form which has a signal peptide and the intracellular form.

## 4. Transcriptional regulation of IL1α, IL1β and IRAP

The structure of the three IL1 gene promoters differ (Fig. 1). The IL1α promoter, unlike those of IL1β and IL1ra, does not have a typical TATA box [2–4]. All three promoters contain NFκB regulatory elements, but only IL1α and IL1β have binding sites for NF-IL6. The IL1β and IL1ra promoters have binding sites for AP1 proteins, cAMP response element binding protein (CREB) and a novel nuclear factor NFβA.

## 5. Biological function

### 5.1. Cellular effects

A full description is given in [1]. IL1 causes leukocyte accumulation by inducing adhesion receptors on vascular endothelium and stimulating chemokine production. It also causes the production of other cytokines, prostanoids and nitric oxide. It stimulates hepatic acute-phase protein synthesis, acts as an accessory signal for lymphocyte activation and is the major endogenous pyrogen. It also regulates extracellular matrices and causes cartilage and bone resorption. A recent study of IL1α/IL1β double knock-out mice [5] demonstrated that IL1 induces its own

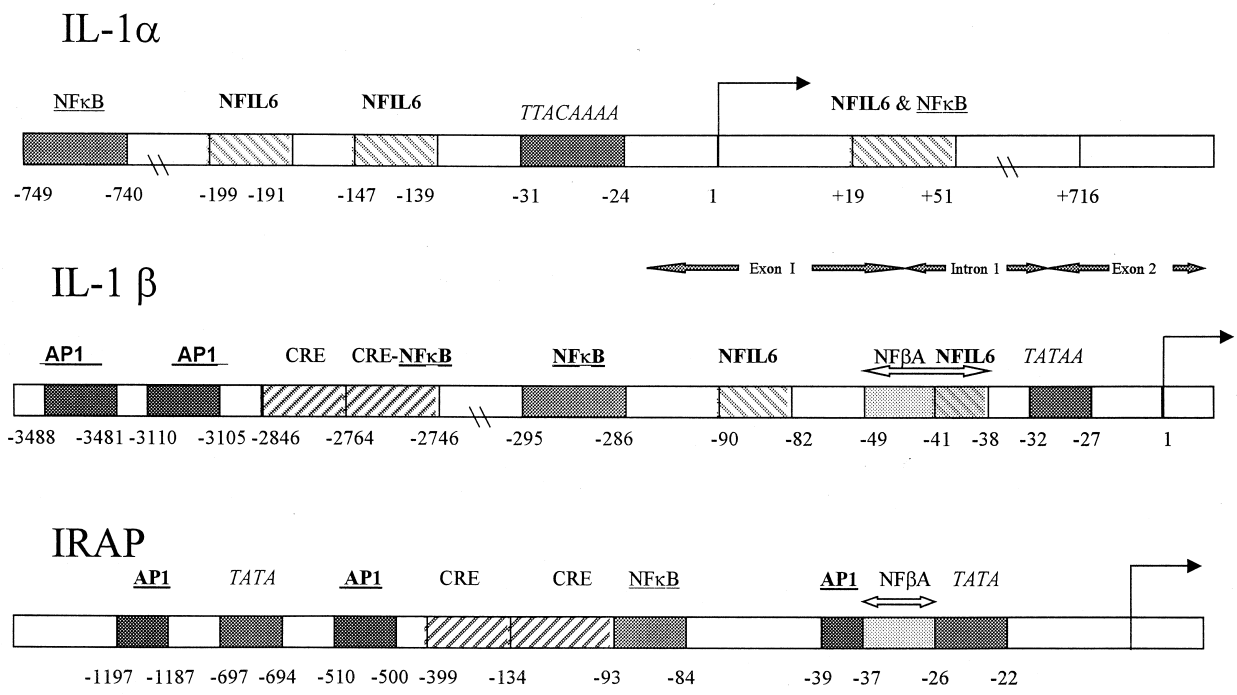


Fig. 1. The IL1 gene promoters. Comparison of the regulatory elements of the IL1α, ILβ and IL1ra promoters. The major transcription factor sites for NFκB (dark blue), NF-IL6 (pink hatched), AP1 (red), cAMP response elements (CRE) that bind CREB (purple hatched), as well as the position of NFβA transcription factor binding elements (light blue) are shown with numbers below each coloured box indicating the boundary of each region and the distance in base pairs from the transcriptional initiation site (shown as an arrow). TATA box sequences (green) are italicised.

expression and that of cyclooxygenase 2 (COX 2) in the brain and is crucial to development of the febrile response. It also increases corticosteroid release through its effect on the hypothalamus.

### 5.2. IL1 receptors

The type I (80 kD) IL1 receptor (IL1RI) transduces the IL1 signal [6] and is widely expressed [1]. The type II receptor (67 kD; IL1R II) is found on B cells, neutrophils and monocytes and preferentially binds IL1β. It may act as a decoy inhibitor of IL1 [7]. The IL1RI has a cytoplasmic tail of 213 amino acids unlike the short 29 amino acid cytoplasmic domain of IL1R II. The IL1R I belongs to a family which includes the IL1 receptor accessory protein (IL1RAcP) [8] and a number of other proteins that do not bind IL1 e.g. Fit1/T1/ST2 (the respective rat/mouse/human homologues) and IL1 receptor-related proteins (IL1Rrp) 1 and 2 ( [9] and references therein). MyD88, rsc 786 and a number of *Drosophila* proteins including *Toll* contain domains homologous to the cytoplasmic tail of IL1R I [9]. The type II receptor is shed from the surface upon cell activation. The soluble form is bound with high affinity by pro and mature forms of β and is an inhibitor of IL1β ( [1] and references therein). Both forms of IL1α but only mature IL1β bind type I receptor.

### 5.3. Signalling

IL1 exerts its effects by inducing expression of many genes whose promoters are regulated through complex interactions with transcription factors such as nuclear factor (NF)κB, AP1, ATF-2 and NF-IL6 ( [10] and references therein). The function of these is modulated via activation of protein kinase cascades by IL1 (Fig. 2). IL-1 generates the sphingomyelin metabolite ceramide [11]. The latter regulates a c-raf activating kinase though its relevance in IL1 signalling is unestablished since IL1 does not activate c-raf.

Binding of IL1α or IL1β to IL1R1 leads to association of a serine/threonine kinase IRAK [12] and the accessory protein (IL1RAcP) with liganded receptor (Fig. 2). IL1RAcP is essential for signalling and may carry IRAK to the receptor [8, 10]. A recent study identified IRAK2 and the death domain-containing MyD88 as part of the signalling receptor complex [13]. How IL1R1 activates downstream kinases is unknown. One cascade leads to phosphorylation of IκB: the inhibitor of NFκB ( [14]; see below). IL1 also activates the three MAP kinase cascades, and a little understood enzyme that is highly specific to IL1 (and also TNF) called TNF and IL1 activated protein kinase or TIPK [15]. It may be a dual specificity kinase since it phosphorylates serine or tyrosine residues in a hydrophobic motif. TNF activates a highly similar profile of kinases to IL1. These pathways are implicated both in the production and action of IL1 and TNF.

### 5.4. MAP kinase pathways

IL1 modulates the three types of mitogen-activated protein (MAP) kinases in mammalian cells ( [10]; see Fig. 2). The first are the p42 and p44 MAPK activated by MKK1 and 2. This pathway is activated by IL1 in cultured fibroblasts, chondrocytes and endothelial cells. Secondly, IL1 activates the c-jun-N-terminal or stress-activated protein kinase (JNK/SAPK) which comprise three closely related genes (JNK 1, 2, 3 or SAPK γ, α, and β respectively). This pathway is activated by IL1 in all responsive cells and in tissues *in vivo*. Thirdly, IL1 activates, in cultured cells, the mammalian homologue of a yeast MAPK: (HOG1) which is activated in response to hyperosmolar conditions. This enzyme, called p38 or reactivating kinase (RK), occurs in two closely related forms, α and β. p38 activates another serine/threonine kinase MAP kinase-activated protein (MAPKAP) kinase-2 which phosphorylates the small heat shock protein hsp 27.

JNK/SAPK is activated by MKK4 and MKK7. The relative importance of these is unknown, but MKK7 is the major activator of JNK/SAPK used by IL1 in liver *in vivo*. p38 activation occurs via MKK6 (Fig. 2). The role of the MAP kinase pathways for particular cell responses has not been established and little is known about relevant downstream targets. What lies upstream of the MKKs is unclear.

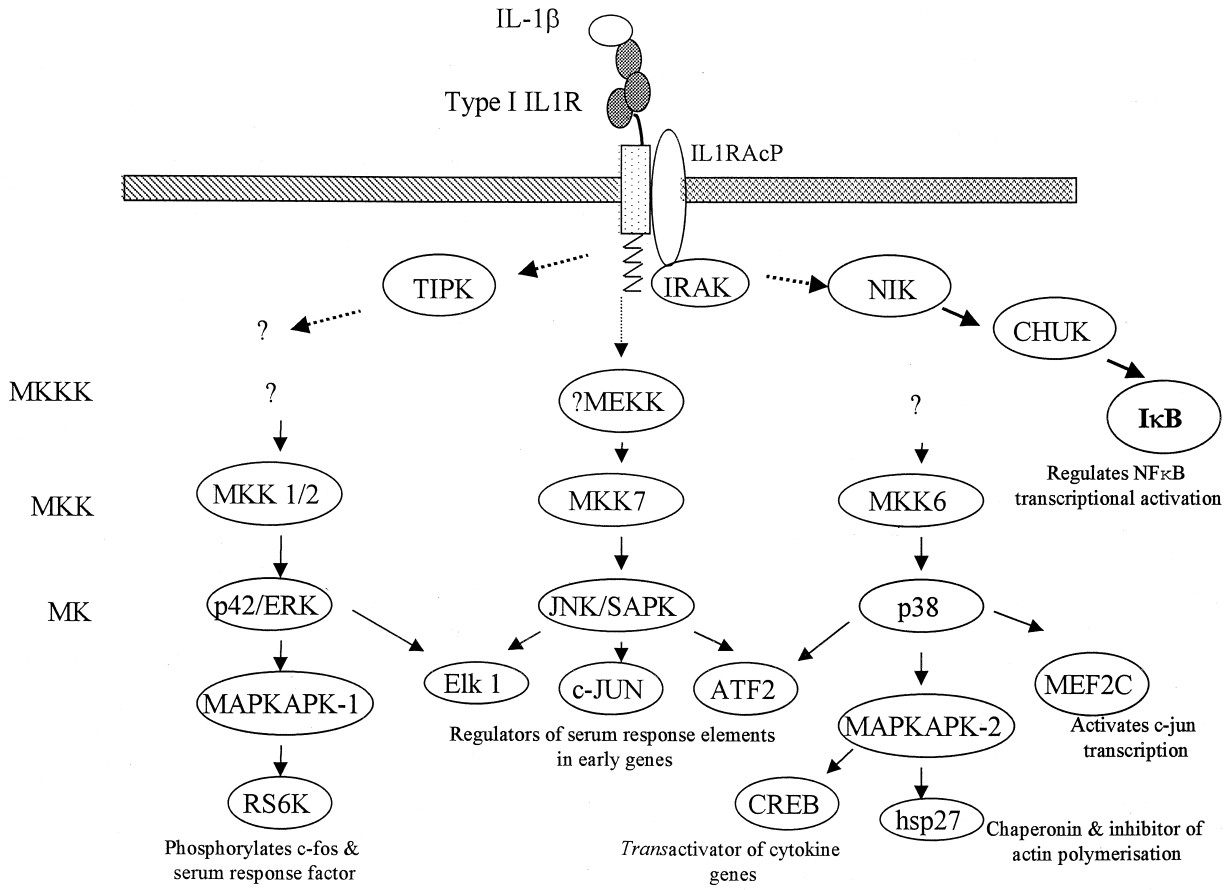


Fig. 2. Signalling events mediated by the type I IL1 receptor. The four major signalling pathways mediated by the type I IL1 receptor are shown. The IκB kinase pathway and the three MAP kinase pathways are detailed. ? indicates the position of unidentified kinases. Functions of the final phosphorylation events in each pathway are shown. Abbreviations of all the kinases, the transcripton factors and other kinase substrates are explained in the text. MK and MAPK stand for MAP kinase. MKK is MAP kinase kinase and MKKK is MAP kinase kinase kinase.

### 5.5. *NFκB pathway*

Activation of the transcription factor NFκB [14] occurs when IκB α and β are degraded by the proteasome following their phosphorylation and ubiquitination. This releases NFκB from IκB, and allows it to enter the nucleus. IκB is phosphorylated upon serines 32 and 36 by IKKα (originally identified as CHUK) and β (Fig. 2). IKK is activated by NFκB inducing kinase (NIK). NIK interacts with the TNF receptor activated factor (TRAF) 2. While no TRAF has been found for IL1RI, dominant negative TRAF 6 inhibits NFκB activation by IL1 [16]. TRAF 6 or a related molecule are therefore implicated in IL1 signalling. The role of IRAK and TRAF 6 in activating downstream kinases is unclear.

### 5.6. *Other transcription factors*

Transcription factors activated by IL1 (other than NFκB) include the known substrates of JNK/SAPK: ATF2 ( [10] and references therein), c-jun, and ternary complex factors such as Elk 1 (Fig. 2). IL1 also activates C/EBP β (NF-IL6) which regulates IL6 and IL8 gene transcription. p38 can phosphorylate a muscle transcription

factor MEF2C and MAPKAP-2 which activates CREB.

### 5.7. Link between kinases and gene expression

Despite increased understanding of the kinase cascades and the transcription factors activated by IL1, the link between these and gene expression remains unclear. One reason for this is the lack of specific pharmacological inhibitors to aid dissection of the pathways. There is a specific inhibitor of p38 which inhibits IL1 induction of COX 2 and matrix metalloproteinases with little effect on production of IL8 or IL6 [10]. This cannot be explained by a selective effect of p38 on known downstream transcription factors since NFκB and NFIL6 regulate the COX 2, IL6 and IL8 genes but not the matrix metalloproteinase gene.

## 6. Role in disease

IL1 is an important mediator in the pathogenesis of many inflammatory and immunologically mediated diseases. One approach to anti-inflammatory therapy is to block its action and phase I clinical trials of soluble type I receptor and IRAP indicate that these have therapeutic effects. Further definition of inflammatory signalling pathways is needed for the identification of new therapeutic targets.

## References

[1] C.A. Dinarello, Biologic basis for interleukin-1 in disease, Blood 87 (1996) 2095–2147.
[2] Y. Furitani, M. Notake, T. Fukui, M. Ohue, H. Nomura, M. Yamada, S. Nakamura, Complete nucleotide sequence of the gene for human interleukin 1 alpha, Nuc. Acids Res. 14 (1986) 3167–3179.
[3] F. Shirakawa, K. Saito, C.A. Bonagura, D.L. Galson, M.J. Fenton, A.C. Webb, P.E. Auron, The human prointerleukin 1β gene requires DNA sequenes both proximal and distal to the transcription start site for tissue-specific induction, Mol. Cell Biol. 13 (1993) 1332–1344.
[4] M.F. Smith, D. Eidlen, M.T. Brewer, S.P. Eisenberg, W.P. Arend, A. Gutierrez-Hartmann, Human IL-1 receptor anatagonist promoter: cell type-specific activity and identification of regulatory regions, J. Immunol. 149 (1992) 2000–2007.
[5] R. Horai, M. Asano, K. Sudo, H. Kanuka, M. Suzuki, M. Nishihara, M. Takahashi, Y. Iwakura, Production of mice deficient in genes for interleukin 1α, IL-1β, IL1α/β, and IL1 receptor antagonist shows that IL1β is crucial in turpentine-induced fever development and glucocorticoid secretion, J. Exp. Med. 187 (1998) 1463–1475.
[6] E. Stylianou, L.A.J. O'Neill, L. Rawlinson, M.R. Edbrooke, P. Woo, J. Saklatvala, Interleukin 1 induces NFκB through its Type I but not Type II receptor in lymphocytes, J. Biol. Chem. 267 (1992) 15836–15841.
[7] F. Colotta, F. Re, M. Muzio et al, Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL4, Science 261 (1993) 472–475.
[8] S.A. Greenfeder, P. Nunes, L. Kwee, M. Labow, R.A. Chizzonite, G. Ju, Molecular cloning and characterisation of a second subunit of the interleukin 1 receptor complex, J. Biol. Chem. 270 (1995) 13757–13765.
[9] J.L. Mitcham, P. Parnet, T.P. Bonnert, K.E. Garka, M.J. Gerhart, J.L. Slack, M.A. Gayle, S.K. Dower, J.E. Sims, T1/ST2 signalling establishes it as a member of an expanding interleukin-1 receptor family, J. Biol. Chem. 271 (1996) 5777–5783.
[10] J. Saklatvala, J. Dean, A. Finch, Protein kinase cascades in intracellular signalling by interleukin 1 and tumour necrosis factor. Biochem. Soc. Trans., in press.
[11] Y. Zhang, B. Yao, S. Delikat, S. Bayoumy, X.-H. Lin, S. Basu, M. McGinley, P.-Y. Chan-Hui, H. Lichenstein, R. Kolesnick, Kinase supressor of ras is ceramide-activated protein kinase, Cell 89 (1997) 63–72.
[12] Z. Cao, W.J. Henzel, X. Gao, IRAK: A kinase associated with the Interleukin-1 receptor, Science 271 (1996) 1128–1131.
[13] M. Muzio, J. Ni, P. Feng, V.M. Dixit, IRAK (Pelle) family member IRAK-2 and MyD88 as proximal mediators of IL-1 signalling, Science 278 (1997) 1612–1615.
[14] I. Stancovski, D. Baltimore, NFκB activation: The IκB kinase revealed? Cell 91 (1997) 299–302.
[15] F. Guesdon, C.G. Knight, L.M. Rawlinson, J. Saklatvala, Dual specificity of the interleukin1 and tumour necrosis factor-activated β casein kinase, J. Biol. Chem. 272 (1997) 30017–30024.
[16] Z. Cao, J. Xiong, M. Takeuchi, T. Kurama, D.V. Goeddel, TRAF6 is a signal transducer for interleukin 1, Nature 383 (1996) 443–446.