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Interleukin-1 (IL-1) Pathway

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The interleukin-1 (IL-1) family of cytokines comprises 11 proteins (IL-1F1 to IL-1F11) encoded by 11 distinct genes in humans and mice. IL-1–type cytokines are major mediators of innate immune reactions, and blockade of the founding members IL-1α or IL-1β by the interleukin-1 receptor antagonist (IL-1RA) has demonstrated a central role of IL-1 in a number of human autoinflammatory diseases. IL-1α or IL-1β rapidly increase messenger RNA expression of hundreds of genes in multiple different cell types. The potent proinflammatory activities of IL-1α and IL-1β are restricted at three major levels: (i) synthesis and release, (ii) membrane receptors, and (iii) intracellular signal transduction. This pathway summarizes extracellular and intracellular signaling of IL-1α or IL-1β, including positive- and negative-feedback mechanisms that amplify or terminate the IL-1 response. In response to ligand binding of the receptor, a complex sequence of combinatorial phosphorylation and ubiquitination events results in activation of nuclear factor κB signaling and the JNK and p38 mitogen-activated protein kinase pathways, which, cooperatively, induce the expression of canonical IL-1 target genes (such as *IL-6, IL-8, MCP-1, COX-2, IκBα, IL-1α, IL-1β, MKP-1*) by transcriptional and posttranscriptional mechanisms. Of note, most intracellular components that participate in the cellular response to IL-1 also mediate responses to other cytokines (IL-18 and IL-33), Toll-like-receptors (TLRs), and many forms of cytotoxic stresses.

Description

IL-1α and IL-1β: Founding members of the IL-1 family. The interleukin-1 (IL-1) family of cytokines comprises 11 proteins (IL-1F1 to IL-1F11) encoded by 11 distinct genes (*IL1A*, *IL1B*, *IL1RN*, *IL18*, and *IL1F5* to *IL1F11* in humans, *Il1A* to *Ilf11* in mice) (*1*–*3*). The main function of IL-1–type cytokines is to control proinflammatory reactions in response to tissue injury by pathogen-associated molecular patterns (PAMPs, such as bacterial or viral products) or damage- or danger-associated molecular patterns released from damaged cells (DAMPs, such as uric acid crystals or adenosine 5′-triphosphate) (*4*–*6*). Thus, they are major mediators of innate immune reactions, and their actions are tightly balanced. The occurrence of severe multiorgan inflammation in patients with homozygous mutations or deletions of the gene encoding interleukin-1 receptor antagonist (IL-1RA) (*7*, *8*) and the successful blockade of inflammatory reactions in humans by application of recombinant IL-1RA (*5*) or antibodies to IL-1β (*9*, *10*) have demonstrated a central role of IL-1α or IL-1β in a number of autoinflammatory diseases (*6*, *11*, *12*). This pathway (Fig. 1) summarizes signaling of the founding members, IL-1α and IL-1β (*13*, *14*), which share only 24% amino acid sequence identity but have largely identical biological function (*1*, *2*, *12*).

Sentinel cells of the innate immune system (macrophages and monocytes) are a major source of IL-1α and IL-1β (*15*–*17*), but many other cell types, including epithelial cells (*18*), endothelial cells (*19*), and fibroblasts (*20*), can also produce IL-1α and IL-β. IL-1α is primarily membrane anchored and signals through autocrine or juxtracrine mechanisms, whereas IL-1β is secreted by an unconventional protein secretion pathway (*21*) and can act in a paracrine manner or systemically (*22*, *23*).

IL-1α and IL-1β rapidly induce the mRNA expression of hundreds of genes in multiple different cell types, such as monocytes or macrophages (*24*, *25*), epithelial (*18*) and endothelial cells (*19*), and chondrocytes (*26*, *27*) or fibroblasts (*20*, *28 29*). In parallel, IL-1α and IL-1β also induce expression of their own genes, which serves as a positive-feedback loop that amplifies the IL-1 response in an autocrine or paracrine manner (*4*, *12*, *15*, *16*, *18*). Stimulation of transcription occurs within 30 min of exposure to IL-1α or IL-1β and can be sustained for many hours (*18*, *28*, *30*). The gene-regulatory actions of IL-1 are transmitted by a conserved signaling system that relies on the rapid, transient, and reversible assembly of multiprotein complexes comprising both nonenzymatic adaptor proteins and enzymes that, once activated, execute sequential phosphorylation and K48-linked degradative or K63-linked nondegradative ubiquitination events.

Owing to their pleiotropic actions, there are three major levels of control to restrict the potent proinflammatory activities of IL-1α and IL-1β: (i) control of synthesis and release by the NALP3-inflammasome [see interpathway links to the Interleukin-1β (IL-1β) Processing Pathway, http://stke.sciencemag.org/cgi/cm/stkecm;CMP_21962], a multiprotein complex that controls activation of the IL-1β–processing protease caspase-1, which was initially called interleukin-1β–converting enzyme (ICE) (*6*, *17*, *31*); (ii) control of the membrane receptors (*23*); and (iii) regulation of the signal transduction downstream of the activated receptors. Regulators at each level are included in the pathway (Fig. 1).

Interleukin-1 receptors. IL-1α and IL-1β independently bind the type I IL-1 receptor (IL-1R1), which is ubiquitously expressed. A third specific ligand, the IL-1 receptor antagonist (IL-1RA), binds the IL-1RI with similar specificity and affinity but does not activate the receptor and trigger downstream signaling (*1*, *32*–*34*). The IL-1 receptor accessory protein (IL-1RAcP) serves as a co-receptor that is required for signal transduction of IL-1/IL-1RI complexes, and this co-receptor is also necessary for activation of IL-1R1 by other IL-1 family members, in particular IL-18 and IL-33 (*1*, *35*–*37*). The type II IL-1 receptor (IL-1R2) binds IL-1α and IL-1β but lacks a signaling-competent cytosolic part and thus serves as a decoy receptor (*23*). The IL-1RA, the plasma membrane–anchored IL-1R2, and the naturally occurring "shed" domains of each of the extracellular IL-1 receptor chains (termed sIL-1RI, sIL-1RII, and sIL-1RAcP, where "s" stands for soluble) provide inducible negative regulators of IL-1 signaling in the extracellular space whose abundance, which is regulated by a combination of increased transcription and controlled release, can limit or terminate IL-1 effects (*23*, *35*).

Receptor-proximal signaling of IL-1. The initial step in IL-1 signal transduction is a ligand-induced conformational change in the first extracellular domain of the

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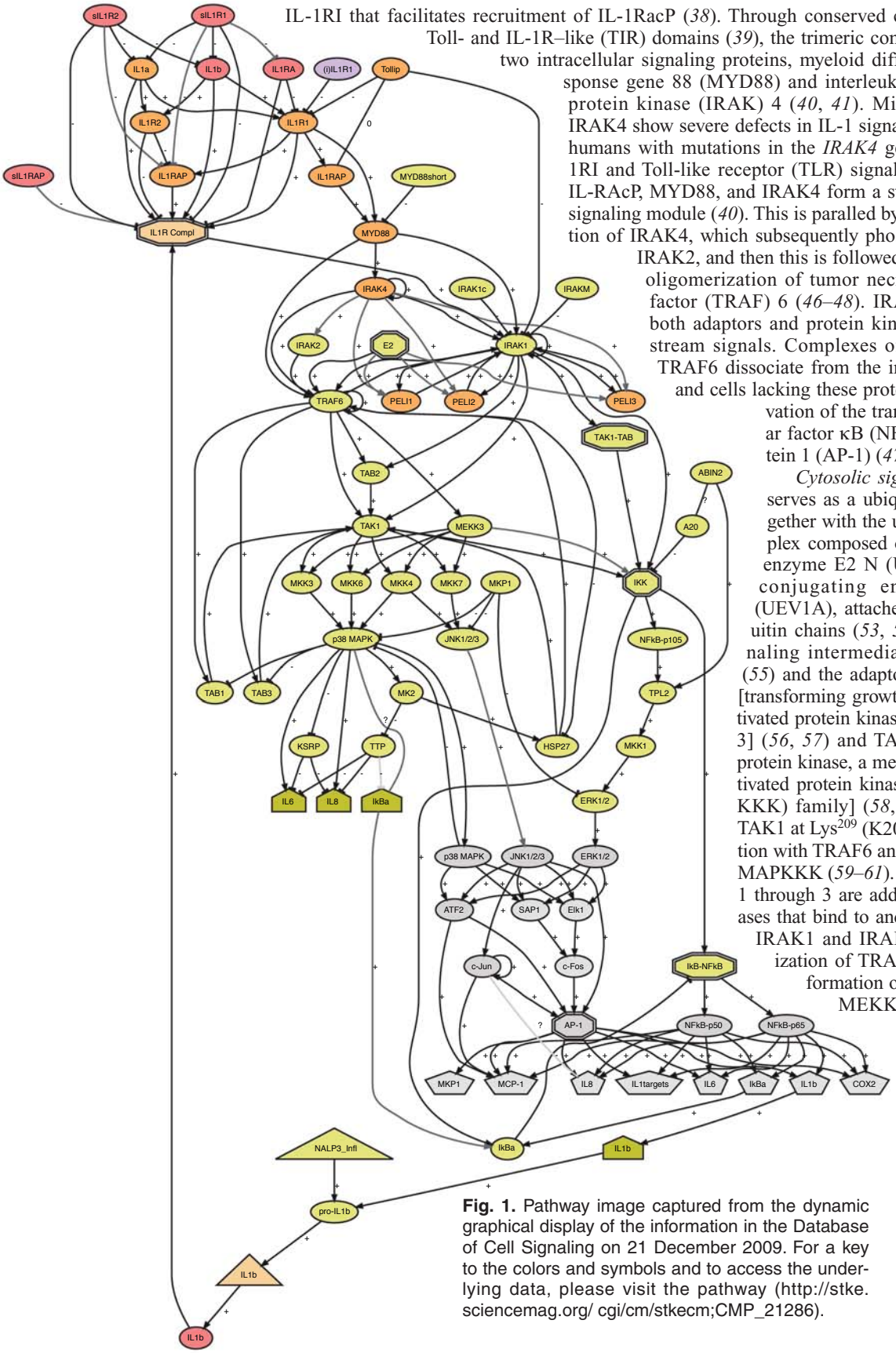

Fig. 1. Pathway image captured from the dynamic graphical display of the information in the Database of Cell Signaling on 21 December 2009. For a key to the colors and symbols and to access the underlying data, please visit the pathway (http://stke.sciencemag.org/ cgi/cm/stkecm;CMP_21286).

IL-1RI that facilitates recruitment of IL-1RacP (*38*). Through conserved cytosolic regions called Toll- and IL-1R–like (TIR) domains (*39*), the trimeric complex rapidly assembles two intracellular signaling proteins, myeloid differentiation primary response gene 88 (MYD88) and interleukin-1 receptor–activated protein kinase (IRAK) 4 (*40*, *41*). Mice lacking MYD88 or IRAK4 show severe defects in IL-1 signaling (*42*–*44*). Similarly, humans with mutations in the *IRAK4* gene have defects in IL-1RI and Toll-like receptor (TLR) signaling (*45*). IL-1, IL-1RI, IL-RAcP, MYD88, and IRAK4 form a stable IL-1–induced first signaling module (*40*). This is paralled by the (auto)phosphorylation of IRAK4, which subsequently phosphorylates IRAK1 and IRAK2, and then this is followed by the recruitment and oligomerization of tumor necrosis factor–associated factor (TRAF) 6 (*46*–*48*). IRAK1 and 2 function as both adaptors and protein kinases to transmit downstream signals. Complexes of IRAK1, IRAK2, and TRAF6 dissociate from the initial receptor complex, and cells lacking these proteins have impaired activation of the transcription factors nuclear factor κB (NF-κB) and activator protein 1 (AP-1) (*47*, *49*–*52*).

Cytosolic signaling of IL-1. TRAF6 serves as a ubiquitin E3 ligase that, together with the ubiquitin E2 ligase complex composed of ubiquitin-conjugating enzyme E2 N (UBC13) and ubiquitin-conjugating enzyme E2 variant 1 (UEV1A), attaches K63-linked polyubiquitin chains (*53*, *54*) to several IL-1–signaling intermediates, including IRAK1 (*55*) and the adaptor proteins TAB2 and 3 [transforming growth factor–β (TGF-β)–activated protein kinase–binding protein 2 and 3] (*56*, *57*) and TAK-1 [TGF-β–activated protein kinase, a member of the mitogen-activated protein kinase kinase kinase (MAPKKK) family] (*58*, *59*). Ubiquitination of TAK1 at Lys^{209} (K209) promotes its association with TRAF6 and with MEKK3, another MAPKKK (*59*–*61*). Pellino homolog (PELI) 1 through 3 are additional ubiquitin E3 ligases that bind to and are phosphorylated by IRAK1 and IRAK4 (*62*–*64*). Oligomerization of TRAF6 (*65*) and subsequent formation of at least two TAK1 and MEKK3 signaling complexes (*59*, *66*) activate the NF-κB, c-Jun N-terminal kinase (JNK), and p38 MAPK pathways (*60*, *67*). Although the exact order of events that link the ubiquitination-dependent associations of IRAKs, TRAF6, PEL1-3, TAK1, and MEKK3 to downstream signaling is not fully resolved yet (*49*), it is

well documented by numerous experimental approaches, including genetics in mice (*60*, *67*) and in *Drosophila* (*68*, *69*), that TAK1 and MEKK3 are core components that link TIR innate immune receptors to gene activation (*4*).

Activation of NF-κB by IL-1 requires the activation of inhibitor of nuclear factor B (IκB) kinase 2 (IKK2) (*70–72*). IKK1 (also called IKKα) and IKK2 (also called IKKβ) plus the regulatory subunit NF-κB essential modifier (NEMO) form the core IKK complex (*73–76*). NEMO binds to polyubiquitin chains on several upstream molecules, including IRAK1 (*77*) and TAK1 bound to either TAB2 or TAB3 (*56*). Activated IKK phosphorylates IκBα, which promotes its K48-linked polyubiquitination and subsequent degradation by the proteasome (*78*, *79*). IκB destruction allows the release of p50 and p65 NF-κB subunits and their nuclear translocation, which is the central step in activation of NF-κB. Both NF-κBs bind to a conserved DNA motif (*80*) that is found in numerous IL-1–responsive genes, in particular the ones encoding IκBα (*81*), IL-6 (*82*), IL-8 (*18*, *83*, *84*), monocyte chemoattractant protein 1 (MCP1) (*28*), and cyclooxygenase 2 (COX2) (*85*). The C terminus of p65 consists of an unstructured potent transactivation domain that induces mRNA synthesis by recruitment of transcriptional coactivators, such as CREB-binding protein (CBP), and of RNA polymerase II (*84*, *86*).

Gene regulation by IL-1. Activation of TAK1 and of MEKK3 also triggers activation of the MAPKKs MKK4, MKK7 (*87–89*), MKK3, and MKK6 (*90*, *91*). MKK4 and MKK7 activate JNK (*30*, *88*, *92–94*), whereas MKK4, MKK3, and MKK6 activate p38 MAPK (*95*, *96*). JNK phosphorylates proteins that are part of AP-1, in particular c-Jun and activating transcription factor 2 (ATF-2) (*97*, *98*). With dominant-negative mutants, antisense RNA, inhibitors, and genetic ablation, it has been shown that JNK and c-Jun play a major role in IL-1–induced expression of genes encoding IL-6 and IL-8 and other IL-1–responsive genes (*18*, *20*, *28*, *30*, *93*). Nuclear p38 MAPK may also activate ATF-2 (*99*). However, in the cytoplasm, a major function of the p38 MAPK pathway is stabilization of otherwise unstable IL-1–responsive mRNAs containing adenine-uridine–rich elements (AREs). *IL-8* (in humans), and *IkBα* and *IL-6* (both in humans and mice), represent three IL-1–inducible transcripts, the abundance of which is rapidly increased by this mechanism in multiple cell types (*89*, *100–103*). p38 MAPK mediates mRNA stabilization and translation of newly made transcripts by inhibiting mRNA-destabilizing factors directly or by activating the downstream kinase MK2 (MAPK-activated protein kinase 2) (*101*). MK2 phosphorylates the destabilizing RNA-binding protein tristetraproline (TTP) (*104*, *105*), whereas p38 MAPK phosphorylates KH-type splicing regulatory protein (KSRP) (*103*, *106*), another mRNA-destabilizing factor that controls the abundance of many IL-1–regulated transcripts (*103*). MK2 also phosphorylates the small heat shock protein HSP27 (*95*, *107*, *108*), which is required for IL-1–induced signaling through TAK1 (*109*, *110*).

Termination of IL-1 signaling. Another conserved feature of the IL-1 signaling pathway is its transient nature. The IL-1R binds the adaptor toll-interacting protein (TOLLIP), which inhibits IRAK1, targets internalized IL-1RI to endosomes, and is required for efficient degradation of IL-1R (*111–113*). IL-1 also activates several negative-feedback inhibitors that shut off IL-1R signaling. p38 MAPK-mediated phosphorylation of TAB1 inactivates TAK1 (*114*); p65 NF-κB-mediated mRNA and protein synthesis of IκBα shuts off the NF-κB response (*115*); and inducible expression of the gene encoding MAPK phosphatase 1 (MKP1) dephosphorylates active MAPKs (*116*, *117*). Some truncated versions of signaling molecules act as "endogenous" dominant-negative inhibitors, such as alternate splice forms of MYD88 (MYD88short) (*118*) or IRAK-1 (IRAK-1c) (*119*). Bacterial lipopolysaccharide (LPS)–induced production of a fourth IRAK family member, IRAK-M, does not activate but rather inhibits IL-1R/Toll-like receptor (TLR)–mediated signaling (*120*).

Conservation of IL-1 signaling mechanisms. Most intracellular components that participate in the cellular response to IL-1 also participate in mediating the response to other cytokines (for example, IL-18 and IL-33, which activate the heterodimeric IL-18α/β and ST2/IL-1RAcP receptors) (*5*, *35*), pathogens (recognized by TLRs) (*4*), and many forms of cytotoxic stresses (*4*). Hence, the IL-1–activated signaling system is truly "canonical." In addition, the NALP3 inflammasome (see specific pathway CMP_21962) that serves to specifically release IL-1 is an evolutionarily conserved, ancient sensor system for many endogenous or exogenous "danger" signals that activate the innate immune system (*6*).

Pathway Details

Scope: Canonical

Pathway URL: http://stke.sciencemag.org/cgi/cm/stkecm;CMP_21286

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