1. Phylogeny:  
   IRAK1 is a highly conserved member of the interleukin‐1 receptor‐associated kinase family that can be traced across all vertebrate species. Within the kinome, IRAK1 groups with other Toll/IL‐1 receptor signal transducers and is evolutionarily related to IRAK4, IRAK2, and the catalytically inactive IRAK-M. Sequence and domain organization analyses have shown that IRAK1 shares the characteristic N-terminal death domain and central kinase domain with its family members, and its conservation from early vertebrates onward indicates its fundamental role in innate immune signaling (janssens2003functionaldiversityand pages 1-2, barbera2012activationmechanismsof pages 33-36). Its phylogenetic relationships, as outlined in large-scale studies of the human kinase complement, place IRAK1 in a kinase subfamily integral to inflammatory response pathways, with evolutionary roots extending to the common ancestor of metazoans (janssens2003functionaldiversityand pages 9-10, barbera2012activationmechanismsof pages 39-41).
2. Reaction Catalyzed:  
   IRAK1 is a serine/threonine-protein kinase that catalyzes the phosphorylation reaction on specific substrate proteins. The reaction can be summarized as follows: ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine phosphate) + H⁺ (woo…2001…analysisof pages 1-2).
3. Cofactor Requirements:  
   The catalytic activity of IRAK1 is dependent on the presence of divalent metal ions, typically Mg²⁺, which facilitates the binding of ATP and the subsequent transfer of the phosphate group to its substrate proteins (woo…2001…analysisof pages 1-2, wang2017crystalstructureof pages 4-5).
4. Substrate Specificity:  
   As a serine/threonine kinase, IRAK1 phosphorylates specific substrates involved in innate immune signaling. In its role in the Toll-like receptor (TLR) and IL-1 receptor (IL-1R) pathways, IRAK1 phosphorylates the E3 ubiquitin ligases known as Pellino proteins (PELI1, PELI2, and PELI3), which then promote subsequent polyubiquitination events required for downstream signaling complex assembly (abudayyeh2008leishmaniainducedirak1inactivation pages 3-4). Furthermore, IRAK1 phosphorylates other substrates such as the adaptor protein TIRAP and the transcription factor IRF7, thereby leading to the activation of NF-κB as well as type I interferon production. Recent high-throughput substrate specificity profiling for human serine/threonine kinases has defined consensus motifs for many kinases; although IRAK1’s precise consensus motif has not been unequivocally established within the context provided, relevant work on serine/threonine kinases suggests a preference for motifs containing basic residues preceding the phosphorylatable serine or threonine (Johnson2023Nature, YaronBarir2024Nature).
5. Structure:  
   The domain organization of IRAK1 consists of an N-terminal death domain, a central kinase domain, and a C-terminal regulatory region. The N-terminal death domain mediates critical interactions with the adaptor protein MyD88, enabling IRAK1 recruitment into the receptor-signaling complex (janssens2003functionaldiversityand pages 2-3). The central kinase domain exhibits the typical bilobal fold observed in serine/threonine kinases, containing an N-terminal lobe that coordinates ATP binding and a C-terminal lobe that houses key catalytic residues. The activation loop within the kinase domain, along with the conserved catalytic residues such as the invariant lysine (K239) and the critical aspartate (e.g., D340), are fundamental for enzymatic activity (woo…2001…analysisof pages 2-3, wang2017crystalstructureof pages 3-4). Crystal structure data, although challenged by limited proteolysis and protein degradation issues as noted in structural studies, indicate that IRAK1 has a more solvent-accessible ATP binding pocket compared to its paralog IRAK4 and contains unique cysteine residues (C302 and C307) in the αD-αE loop. These cysteine residues constitute potential covalent inhibitor targets and contribute to differences in inhibitor specificity, as evidenced by species-specific sensitivity to compounds such as JNK-IN-7 (wang2017crystalstructureof pages 3-4, 4-5). In addition, an insertion in the activation loop forms a partially resolved helix (designated αGH), and the presence of a bulky gatekeeper residue further contributes to its unique inhibitor binding characteristics (wang2017crystalstructureof pages 3-4).
6. Regulation:  
   IRAK1 activity is tightly regulated through multiple post-translational modifications and protein–protein interactions. Its activation is initiated by recruitment to the activated IL-1 or Toll-like receptor complex by MyD88, where it is phosphorylated by IRAK4 on specific residues and subsequently undergoes autophosphorylation. This phosphorylation cascade results in conformational changes that are essential for the full activation of IRAK1 (woo…2001…analysisof pages 1-2, vollmer2017themechanismof pages 3-5). Furthermore, IRAK1 is subject to ubiquitination by E3 ubiquitin ligases, such as Pellino proteins, which are activated by IRAK1-mediated phosphorylation; polyubiquitination events are necessary for recruiting downstream signaling complexes including the TAK1–TRAF6 and the IKK complexes (abudayyeh2008leishmaniainducedirak1inactivation pages 8-9). Negative regulation of IRAK1 is mediated by dephosphorylation reactions through protein tyrosine phosphatases like SHP-1. SHP-1 binds directly to IRAK1 via a highly conserved kinase tyrosyl-based inhibitory motif (KTIM) present exclusively in IRAK1 among the IRAK family members, leading to rapid and sustained inhibition of its kinase activity. This mechanism is exploited by pathogens such as Leishmania to suppress macrophage activation during infection (abudayyeh2008leishmaniainducedirak1inactivation pages 3-4, abudayyeh2008leishmaniainducedirak1inactivation pages 4-5, dayyeh2009alterationofmacrophage pages 137-143). Additionally, sumoylation of IRAK1 can induce its nuclear translocation where it phosphorylates transcription factors like STAT3, thereby adding an extra layer of regulation and functional diversification (information section).
7. Function:  
   IRAK1 plays a central role in initiating innate immune responses against pathogens. Upon Toll-like receptor (TLR) or interleukin-1 receptor (IL-1R) activation, IRAK1 is recruited by the adaptor MyD88 to the receptor-signaling complex, where it is phosphorylated by IRAK4 and self-activates through autophosphorylation. Fully active IRAK1 then phosphorylates downstream targets, notably the Pellino family of E3 ubiquitin ligases. The polyubiquitination of IRAK1 facilitates the assembly of large signaling complexes that include MAP3K7/TAK1, TRAF6, and the IKK complex, ultimately leading to the activation of the NF-κB and MAP kinase pathways. This cascade results in transcriptional induction of pro-inflammatory cytokines (such as TNF-α, IL-12, and IL-1β), as well as the induction of type I interferon genes via IRF7 phosphorylation. In addition, IRAK1 phosphorylates TIRAP, promoting its ubiquitination and degradation, which modulates the duration and magnitude of TLR signaling (abudayyeh2008leishmaniainducedirak1inactivation pages 8-9, dayyeh2009alterationofmacrophage pages 137-143). In some contexts, when sumoylated, IRAK1 translocates to the nucleus to phosphorylate STAT3, thereby linking innate immune stimulation to transcriptional programs involved in antiviral defense and other cellular processes. IRAK1 is prominently expressed in immune cells such as monocytes, macrophages, and dendritic cells, where its activity is essential for effective host defense against pathogens. Furthermore, the dysregulation of IRAK1 activity is associated with altered inflammatory responses and is implicated in pathology related to immunodeficiency, autoimmunity, and even certain cancers (dayyeh2009alterationofmacrophage pages 121-127, janssens2003functionaldiversityand pages 9-10).
8. Other Comments:  
   Several small-molecule inhibitors targeting IRAK1 have been identified, with compounds such as JNK-IN-7 demonstrating inhibitory activity by covalently modifying a key cysteine (C302) in the kinase domain. This inhibition exhibits species-specific differences due to variations in residue composition at the inhibitor binding site (wang2017crystalstructureof pages 4-5, vollmer2017themechanismof pages 8-10). IRAK1 is exploited by pathogens such as Leishmania, which activate SHP-1 phosphatase to bind IRAK1 via its KTIM motif and thereby suppress macrophage inflammatory responses. Additionally, altered IRAK1 signaling has been linked to various inflammatory disorders and may contribute to oncogenic processes when aberrantly activated. Comprehensive analyses of IRAK1’s role in immune responses continue to underline its importance as a potential therapeutic target. Notable contributions in the substrate specificity of serine/threonine kinases, as well as evolutionary analyses of the kinome, have provided further context for understanding IRAK1’s place within the human kinase complement (Johnson2023Nature, Manning2002Science).
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