**Accepted name:** Interleukin‑1 receptor‑associated kinase 1 (IRAK1) – Gene: IRAK1 (Uniprot: P51617)  
**Synonyms:** IRAK, IRAK‑1

1. Phylogeny  
   IRAK1 is a serine/threonine kinase that is a central member of the IRAK family, a distinct subgroup within the human kinome responsible for transducing signals from Toll‑like receptors (TLRs) and interleukin‑1 receptors (IL‑1Rs) (bahia2015interleukin1receptorassociated pages 17-17). Evolutionary analyses indicate that IRAK1 is highly conserved across mammalian species and that orthologs of IRAK1 are present in a variety of vertebrate lineages, including fish, amphibians, reptiles, birds, and mammals. This widespread conservation reflects the ancient origin of IRAK1 as an indispensable element of innate immunity (flannery2010theinterleukin1receptorassociated pages 24-28). Within the IRAK family, four members are recognized in humans: IRAK1, IRAK2, IRAK3 (also known as IRAK‑M), and IRAK4. Although all of these proteins share a conserved domain organization that includes an N‑terminal death domain and a central kinase domain, IRAK1 distinguishes itself through its high catalytic activity and unique interaction surfaces with the signaling adaptor MyD88 (dardick2006plantandanimal pages 3-6). Comparative phylogenetic studies, inspired by the pioneering work of Manning and colleagues, have revealed that the IRAK family proteins emerged from gene duplication events early in the evolution of vertebrates. Subsequent functional specialization among these paralogs has resulted in IRAK1 maintaining robust kinase activity while other members, such as IRAK3, have evolved primarily negative regulatory roles (ringwood2008theinvolvementof pages 1-2). In this way, IRAK1 occupies a central and evolutionarily ancient position within an immune signaling module that is indispensable for host defense.
2. Reaction Catalyzed  
   IRAK1 catalyzes the ATP‐dependent phosphorylation of protein substrates specifically on serine and threonine residues. In this capacity, the kinase transfers the terminal (γ) phosphate group from ATP to the hydroxyl group on the side chains of serine or threonine residues present in its target proteins. The overall chemical reaction can be summarized as:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This phosphorylation event is fundamental to IRAK1’s role in propagating downstream signaling events in the innate immune response, ultimately leading to modifications in the activity or stability of those substrates (flannery2010theinterleukin1receptorassociated pages 24-28).
3. Cofactor Requirements  
   Similar to canonical serine/threonine kinases, IRAK1 requires the presence of divalent metal ions to facilitate its catalytic activity. In particular, magnesium ions (Mg²⁺) are essential for ATP binding within the active site. The Mg²⁺ ion coordinates with the phosphates of ATP to correctly orient the γ-phosphate for efficient transfer onto the serine/threonine residue of the substrate. This metal ion requirement is a characteristic feature of the kinase catalytic mechanism and is critical for ensuring the high-fidelity phosphotransfer reaction that underpins IRAK1’s signaling role (bahia2015interleukin1receptorassociated pages 17-17).
4. Substrate Specificity  
   IRAK1 exhibits a substrate specificity that underlies its ability to modulate key components in the innate immune signaling cascade. One prominent group of substrates for IRAK1 consists of the E3 ubiquitin ligases collectively known as the Pellino protein family, which includes PELI1, PELI2, and PELI3. Phosphorylation of these Pellino proteins by IRAK1 plays a critical role in triggering their E3 ligase activity, which in turn leads to K63-linked polyubiquitination of IRAK1. This polyubiquitination serves as a signal amplification mechanism, facilitating the formation of a signaling complex that integrates additional downstream components (bossart2025quantitativeproteomicsof pages 95-97).  
   Additionally, IRAK1 phosphorylates the Toll/IL-1 receptor domain-containing adaptor protein (TIRAP). Phosphorylation of TIRAP primes it for ubiquitination and subsequent proteasomal degradation, thereby contributing to the negative feedback regulation of the receptor signal. Another significant substrate is interferon regulatory factor 7 (IRF7); phosphorylation of IRF7 by IRAK1 is essential for its activation and subsequent translocation to the nucleus, where it induces the expression of type I interferon genes (flannery2010theinterleukin1receptorassociated pages 32-35).  
   Furthermore, when IRAK1 undergoes sumoylation, it translocates into the nucleus, enabling it to phosphorylate the transcription factor STAT3. Phosphorylation of STAT3 influences the transcription of genes involved in cell survival and inflammatory responses (balasuriya2020phosphorylationdependentsubstrateselectivity pages 3-5).  
   Although a strictly defined consensus phosphorylation motif for IRAK1 has not been fully characterized, its substrate repertoire clearly shows a preference for key regulatory proteins that modulate both inflammatory and antiviral responses.
5. Structure  
   IRAK1 is a multidomain protein whose structural organization facilitates its role as both a kinase and an adaptor in immune signaling. The most N‑terminal segment of IRAK1 contains the death domain (DD), which is critical for mediating homotypic protein–protein interactions with the adaptor MyD88. This DD is indispensable for the rapid recruitment of IRAK1 to activated TLR or IL‑1 receptor complexes in the early phases of signal transduction (flannery2010theinterleukin1receptorassociated pages 5-9).  
   Centrally, IRAK1 harbors a highly conserved serine/threonine kinase domain that exhibits the classic bilobal architecture common among eukaryotic protein kinases. The N-terminal lobe of this domain is predominantly composed of β-sheets and is relatively small compared to the larger C-terminal lobe, which is rich in α-helical structures (gosu2014structuraldynamicanalysis pages 11-12). These lobes are connected by a flexible hinge region, forming the ATP-binding pocket that coordinates the necessary Mg²⁺-ATP complex.  
   Within the kinase domain, several critical structural motifs facilitate catalytic activity. The glycine-rich loop, located in the N-terminal lobe, is essential for proper positioning of ATP by allowing the required flexibility and stabilization of the phosphate groups. Adjacent to this, the catalytic loop contains key residues that contribute to the phosphate transfer mechanism. The activation loop, a flexible segment that undergoes phosphorylation, further regulates the conformational state of the kinase and its transition to an active state upon receiving phosphorylation signals from upstream kinases – notably IRAK4 – as well as via autophosphorylation events (flannery2010theinterleukin1receptorassociated pages 9-13).  
   Another important element within the kinase domain is the conserved C-helix, which plays a role in aligning the active site residues necessary for phosphotransfer. Collectively, these sub-structures, including the catalytic and activation loops and the C-helix, form what is known as the catalytic spine and hydrophobic core, ensuring both the stability and functional competence of the kinase domain.  
   Although full-length high-resolution crystal structures of IRAK1 are not yet available, homology models derived from related kinases, particularly IRAK4, have provided significant insights regarding the spatial arrangement of its domains. These models suggest that IRAK1, in addition to its kinase core, houses regulatory regions that are potential targets for post-translational modifications such as ubiquitination and sumoylation. Sequence analysis also implies the presence of nuclear localization signals embedded within its non-catalytic regions, which become accessible upon specific modifications like sumoylation, thus permitting nuclear translocation under defined cellular conditions (gosu2014structuraldynamicanalysis pages 12-12, reinhardt2023acriticalevaluation pages 26-27).
6. Regulation  
   The regulatory mechanisms governing IRAK1 activity are multi-tiered and rely on an intricate network of post-translational modifications and protein–protein interactions. In response to the engagement of TLRs or IL‑1Rs, the adaptor protein MyD88 recruits IRAK1 to the receptor complex via interactions through the death domain (flannery2010theinterleukin1receptorassociated pages 1-5). Once localized to the receptor complex, IRAK1 is phosphorylated by the upstream kinase IRAK4 on key serine and threonine residues within its activation loop, an event that is crucial for priming IRAK1 and enabling its subsequent autophosphorylation (bahia2015interleukin1receptorassociated pages 17-17, rhyasen2015iraksignallingin pages 1-2).  
   Post-activation, IRAK1 establishes further layers of regulation through its ability to phosphorylate downstream targets. One critical event is the phosphorylation of the Pellino family of E3 ubiquitin ligases. This phosphorylation facilitates K63-linked polyubiquitination of IRAK1, creating a platform for the binding of ubiquitin-binding proteins such as NEMO (IKBKG) and promoting the assembly of multiprotein signaling complexes that ultimately lead to NF‑κB activation (bossart2025quantitativeproteomicsof pages 95-97).  
   Concomitantly, IRAK1 phosphorylates the adaptor TIRAP, a modification that primes TIRAP for ubiquitination and subsequent proteasomal degradation, thereby providing a negative feedback loop that helps to attenuate prolonged receptor signaling (flannery2010theinterleukin1receptorassociated pages 32-35, ringwood2008theinvolvementof pages 1-2).  
   A further level of control is exerted via sumoylation of IRAK1. Upon sumoylation, IRAK1 is capable of translocating from the cytosol to the nucleus where it phosphorylates the transcription factor STAT3, thus linking acute immunoregulatory signaling events with longer-term modifications in gene expression (scarneo2020ahighlyselective pages 1-2).  
   Together, these modifications – including IRAK4-mediated phosphorylation, IRAK1 autophosphorylation, ubiquitination driven by Pellino ligases, and sumoylation – enable a tightly controlled, spatially and temporally regulated activation of IRAK1 within the innate immune response (reinhardt2023acriticalevaluation pages 26-27).
7. Function  
   IRAK1 is a pivotal mediator in the innate immune system, serving as a crucial link between receptor activation and the downstream signaling cascades that regulate inflammation and antiviral responses. Upon recognition of pathogen-associated molecular patterns (PAMPs) by Toll‑like receptors or the binding of interleukin‑1 to its receptor, MyD88 recruits IRAK1 to the receptor complex where it undergoes phosphorylation by IRAK4. This event initiates a cascade of phosphorylation events that amplify the immune signal (bahia2015interleukin1receptorassociated pages 17-17).  
   One primary role of activated IRAK1 is the phosphorylation of Pellino proteins, a family of E3 ubiquitin ligases. This phosphorylation triggers the polyubiquitination of IRAK1 itself, which in turn promotes the recruitment and assembly of a large signaling complex that includes MAP3K7/TAK1, TRAF6, and the regulatory NEMO-IKK complex. The formation of this signaling complex is essential for the activation of the IKK kinases (IKKA/CHUK and IKBKB), leading to the nuclear translocation of NF‑κB. Once in the nucleus, NF‑κB activates a wide array of inflammatory cytokine genes, thereby driving the inflammatory response (bossart2025quantitativeproteomicsof pages 95-97).  
   In parallel, IRAK1 phosphorylates TIRAP, which promotes the subsequent ubiquitination and degradation of this adaptor protein, a process that modulates the magnitude and duration of the immune signaling by providing an inherent negative feedback mechanism (flannery2010theinterleukin1receptorassociated pages 32-35).  
   In addition to controlling proinflammatory pathways, IRAK1 is also integral to antiviral defense. It achieves this by phosphorylating interferon regulatory factor 7 (IRF7). Phosphorylated IRF7 translocates to the nucleus where it stimulates the transcription of type I interferon genes, leading to the establishment of an antiviral state within the cell (flannery2010theinterleukin1receptorassociated pages 32-35).  
   Furthermore, IRAK1’s function is expanded when it is modified by sumoylation; once sumoylated, IRAK1 translocates to the nucleus, where it is capable of phosphorylating STAT3. The phosphorylation of STAT3 is associated with the regulation of genes involved in cell survival, proliferation, and additional aspects of immune modulation (scarneo2020ahighlyselective pages 1-2).  
   Expression of IRAK1 is predominantly observed in cells of the innate immune system – such as macrophages, dendritic cells, and lymphocytes – but it is also expressed in various non-immune tissues, indicating a broader physiological relevance. In these diverse cellular contexts, IRAK1 functions both as an active kinase initiating signal transduction and as a scaffold that brings together different signaling molecules within the Myddosome complex (bennett2022irak1andirak4 pages 1-2).
8. Other Comments  
   IRAK1 has been the subject of extensive research owing to its central role in initiating and modulating the immune response, and its dysregulation has been implicated in a range of pathological conditions including autoimmune diseases, chronic inflammatory disorders, and hematologic malignancies. For instance, aberrant activation or overexpression of IRAK1 has been linked with enhanced NF‑κB signaling and is observed in conditions where chronic inflammation is a driving factor (rhyasen2014irakfamilykinases pages 115-119).  
   Therapeutically, IRAK1 is being actively pursued as a target for drug development. Several experimental inhibitors that target the IRAK1/IRAK4 kinase axis have shown antiproliferative effects in preclinical models, particularly in the context of MYD88-mutated B-cell lymphomas, wherein constitutive IRAK signaling supports tumor survival. The highly conserved nature of the ATP-binding pocket between IRAK1 and IRAK4 presents challenges for the development of selective inhibitors; nonetheless, selective inhibition strategies have been reported that discriminate between these kinases enough to delineate their individual signaling roles (scarneo2020ahighlyselective pages 1-2, hatcher2020discoveryofa pages 5-6).  
   Moreover, research has emphasized the dual role of IRAK1. Beyond its catalytic function, IRAK1 can serve as a scaffolding protein within the Myddosome, meaning that strategies solely focused on kinase inhibition might not fully abrogate IRAK1-dependent signaling. Consequently, further understanding of its non-catalytic roles is of considerable interest, particularly in the development of comprehensive therapeutic approaches.  
   The modulation of IRAK1 activity by post-translational modifications such as ubiquitination and sumoylation not only underscores its multifaceted roles within the cell but also suggests that interventions aimed at modifying these regulatory processes may offer alternative therapeutic benefits. Genetic studies have identified polymorphisms and somatic alterations in IRAK1 associated with altered immune responses, suggesting that in addition to chemical inhibitors, gene-based therapeutic methods might also be developed in the future to target aberrant IRAK1 signaling (rhyasen2015iraksignallingin pages 1-2).
9. References

* bahia2015interleukin1receptorassociated pages 17-17
* balasuriya2020phosphorylationdependentsubstrateselectivity pages 3-5
* bennett2022irak1andirak4 pages 1-2
* bossart2025quantitativeproteomicsof pages 95-97
* dardick2006plantandanimal pages 3-6
* flannery2010theinterleukin1receptorassociated pages 1-5, 24-28, 32-35, 5-9, 9-13
* gosu2014structuraldynamicanalysis pages 11-12, 12-12
* reinhardt2023acriticalevaluation pages 26-27
* ringwood2008theinvolvementof pages 1-2
* rhyasen2014irakfamilykinases pages 115-119
* scarneo2020ahighlyselective pages 1-2
* hatcher2020discoveryofa pages 5-6
* rhyasen2015iraksignallingin pages 1-2

References

1. (bahia2015interleukin1receptorassociated pages 17-17): Malkeet Singh Bahia, Maninder Kaur, Pragati Silakari, and Om Silakari. Interleukin-1 receptor associated kinase inhibitors: potential therapeutic agents for inflammatory- and immune-related disorders. Cellular Signalling, 27:1039-1055, Jun 2015. URL: https://doi.org/10.1016/j.cellsig.2015.02.025, doi:10.1016/j.cellsig.2015.02.025. This article has 57 citations and is from a peer-reviewed journal.
2. (balasuriya2020phosphorylationdependentsubstrateselectivity pages 3-5): Nileeka Balasuriya, Norman E. Davey, Jared L. Johnson, Huadong Liu, Kyle K. Biggar, Lewis C. Cantley, Shawn Shun-Cheng Li, and Patrick O’Donoghue. Phosphorylation-dependent substrate selectivity of protein kinase b (akt1). Journal of Biological Chemistry, 295:8120-8134, Jun 2020. URL: https://doi.org/10.1074/jbc.ra119.012425, doi:10.1074/jbc.ra119.012425. This article has 50 citations and is from a domain leading peer-reviewed journal.
3. (bennett2022irak1andirak4 pages 1-2): Joshua Bennett and Daniel T. Starczynowski. Irak1 and irak4 as emerging therapeutic targets in hematologic malignancies. Current Opinion in Hematology, 29:8-19, Nov 2022. URL: https://doi.org/10.1097/moh.0000000000000693, doi:10.1097/moh.0000000000000693. This article has 77 citations and is from a peer-reviewed journal.
4. (bossart2025quantitativeproteomicsof pages 95-97): J Bossart. Quantitative proteomics of human immune cells for defining their roles in disease development and treatment response. Unknown journal, 2025.
5. (dardick2006plantandanimal pages 3-6): Christopher Dardick and Pamela Ronald. Plant and animal pathogen recognition receptors signal through non-rd kinases. PLoS Pathogens, 2:e2, Jan 2006. URL: https://doi.org/10.1371/journal.ppat.0020002, doi:10.1371/journal.ppat.0020002. This article has 323 citations and is from a highest quality peer-reviewed journal.
6. (flannery2010theinterleukin1receptorassociated pages 1-5): Sinead Flannery and Andrew G. Bowie. The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling. Biochemical Pharmacology, 80:1981-1991, Dec 2010. URL: https://doi.org/10.1016/j.bcp.2010.06.020, doi:10.1016/j.bcp.2010.06.020. This article has 392 citations and is from a domain leading peer-reviewed journal.
7. (flannery2010theinterleukin1receptorassociated pages 24-28): Sinead Flannery and Andrew G. Bowie. The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling. Biochemical Pharmacology, 80:1981-1991, Dec 2010. URL: https://doi.org/10.1016/j.bcp.2010.06.020, doi:10.1016/j.bcp.2010.06.020. This article has 392 citations and is from a domain leading peer-reviewed journal.
8. (flannery2010theinterleukin1receptorassociated pages 32-35): Sinead Flannery and Andrew G. Bowie. The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling. Biochemical Pharmacology, 80:1981-1991, Dec 2010. URL: https://doi.org/10.1016/j.bcp.2010.06.020, doi:10.1016/j.bcp.2010.06.020. This article has 392 citations and is from a domain leading peer-reviewed journal.
9. (flannery2010theinterleukin1receptorassociated pages 5-9): Sinead Flannery and Andrew G. Bowie. The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling. Biochemical Pharmacology, 80:1981-1991, Dec 2010. URL: https://doi.org/10.1016/j.bcp.2010.06.020, doi:10.1016/j.bcp.2010.06.020. This article has 392 citations and is from a domain leading peer-reviewed journal.
10. (flannery2010theinterleukin1receptorassociated pages 9-13): Sinead Flannery and Andrew G. Bowie. The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling. Biochemical Pharmacology, 80:1981-1991, Dec 2010. URL: https://doi.org/10.1016/j.bcp.2010.06.020, doi:10.1016/j.bcp.2010.06.020. This article has 392 citations and is from a domain leading peer-reviewed journal.
11. (gosu2014structuraldynamicanalysis pages 11-12): Vijayakumar Gosu and Sangdun Choi. Structural dynamic analysis of apo and atp-bound irak4 kinase. Scientific Reports, Jul 2014. URL: https://doi.org/10.1038/srep05748, doi:10.1038/srep05748. This article has 41 citations and is from a poor quality or predatory journal.
12. (gosu2014structuraldynamicanalysis pages 12-12): Vijayakumar Gosu and Sangdun Choi. Structural dynamic analysis of apo and atp-bound irak4 kinase. Scientific Reports, Jul 2014. URL: https://doi.org/10.1038/srep05748, doi:10.1038/srep05748. This article has 41 citations and is from a poor quality or predatory journal.
13. (hatcher2020discoveryofa pages 5-6): John M. Hatcher, Guang Yang, Li Wang, Scott B. Ficarro, Sara Buhrlage, Hao Wu, Jarrod A. Marto, Steven P. Treon, and Nathanael S. Gray. Discovery of a selective, covalent irak1 inhibitor with antiproliferative activity in myd88 mutated b-cell lymphoma. ACS Medicinal Chemistry Letters, 11:2238-2243, Oct 2020. URL: https://doi.org/10.1021/acsmedchemlett.0c00378, doi:10.1021/acsmedchemlett.0c00378. This article has 23 citations and is from a peer-reviewed journal.
14. (reinhardt2023acriticalevaluation pages 26-27): Ronja Reinhardt and Thomas A Leonard. A critical evaluation of protein kinase regulation by activation loop autophosphorylation. eLife, Jul 2023. URL: https://doi.org/10.7554/elife.88210, doi:10.7554/elife.88210. This article has 43 citations and is from a domain leading peer-reviewed journal.
15. (rhyasen2014irakfamilykinases pages 115-119): GW Rhyasen. Irak family kinases as therapeutic targets for myelodysplastic syndrome and acute myeloid leukemia. Unknown journal, 2014.
16. (rhyasen2015iraksignallingin pages 1-2): Garrett W. Rhyasen, Garrett W. Rhyasen, Garrett W. Rhyasen, D. Starczynowski, and D. Starczynowski. Irak signalling in cancer. British Journal of Cancer, 112:232-237, Oct 2015. URL: https://doi.org/10.1038/bjc.2014.513, doi:10.1038/bjc.2014.513. This article has 198 citations and is from a domain leading peer-reviewed journal.
17. (ringwood2008theinvolvementof pages 1-2): Lorna Ringwood and Liwu Li. The involvement of the interleukin-1 receptor-associated kinases (iraks) in cellular signaling networks controlling inflammation. Cytokine, 42:1-7, Apr 2008. URL: https://doi.org/10.1016/j.cyto.2007.12.012, doi:10.1016/j.cyto.2007.12.012. This article has 104 citations and is from a peer-reviewed journal.
18. (scarneo2020ahighlyselective pages 1-2): Scott A. Scarneo, Philip F. Hughes, Kelly W. Yang, David A. Carlson, Deepak Gurbani, Kenneth D. Westover, and Timothy A.J. Haystead. A highly selective inhibitor of interleukin-1 receptor–associated kinases 1/4 (irak-1/4) delineates the distinct signaling roles of irak-1/4 and the tak1 kinase. Journal of Biological Chemistry, 295:1565-1574, Feb 2020. URL: https://doi.org/10.1074/jbc.ra119.011857, doi:10.1074/jbc.ra119.011857. This article has 30 citations and is from a domain leading peer-reviewed journal.