1. Phylogeny  
   IRAK2 is a member of the interleukin‑1 receptor‑associated kinase (IRAK) family, which in mammals comprises four principal members: IRAK1, IRAK2, IRAK‑M (also known as IRAK3), and IRAK4. Phylogenetic analyses reveal that IRAK2 is evolutionarily related to both IRAK1 and IRAK4, and its lineage appears to have originated through gene duplication events from an ancestral IRAK4‑like kinase present early in vertebrate evolution (benosman2013interleukin1receptorassociatedkinase2 pages 3-3, gosu2012molecularevolutionand pages 1-2). Orthologs of IRAK2 are widely conserved in mammals, and comparable proteins have been identified in invertebrates such as Drosophila, where the homolog Tube performs analogous functions in Toll‑mediated immune signaling. Sequence comparisons across species indicate that the catalytic regions, including the central kinase domain and the protein–protein interaction modules such as the death domain, are highly conserved among the IRAK family. In particular, IRAK2 is classified as a non‑RD kinase, which means that unlike typical RD kinases it lacks the conserved arginine residue immediately preceding the catalytic aspartate in the activation segment. This non‑RD feature is shared with several kinases that have evolved to serve more in scaffolding or regulatory roles rather than providing robust catalytic activity in classical phosphorylation reactions (biswas2007myeloiddifferentiationfactor pages 4-5, dardick2006plantandanimal pages 6-7). Furthermore, multiple analyses of its domain structure and sequence homology imply that although IRAK2 may exhibit lower intrinsic catalytic activity compared to other kinases, its evolutionarily conserved domains reflect its indispensability in the assembly of multi‑protein complexes, such as the Myddosome, that are critical for downstream signal transduction in innate immunity (gosu2012molecularevolutionand pages 14-15, maschera1999overexpressionofan pages 4-5).
2. Reaction Catalyzed  
   IRAK2 functions in a manner characteristic of serine/threonine protein kinases. The reaction catalyzed by IRAK2 involves the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues on substrate proteins. In this phosphorylation reaction, ATP and a protein substrate that possesses accessible serine or threonine residues are converted into ADP and a phosphorylated form of the substrate, along with the release of a proton (H⁺). The chemical reaction may be summarized as: ATP + [protein]-(L‑serine or L‑threonine) → ADP + [protein]-(L‑serine/threonine)-phosphate + H⁺. Although certain isoforms or contexts have led to the categorization of IRAK2 as having noncanonical kinase activity, the catalytic event that IRAK2 is thought to mediate, at least by analogy to other serine/threonine kinases, is the aforementioned phosphoryl transfer (benosman2013interleukin1receptorassociatedkinase2 pages 1-3).
3. Cofactor Requirements  
   Consistent with the general mechanism of protein kinases, IRAK2’s catalytic activity is dependent on binding divalent cations that help coordinate the ATP molecule necessary for the phosphoryl transfer. In particular, Mg²⁺ ions serve as a crucial cofactor for IRAK2, as they facilitate the proper positioning of ATP within the active site and stabilize the negative charges that develop during the transition state of the reaction. This requirement for Mg²⁺ is a universal property observed in most kinases and is essential for catalytic function in a cellular context (wang2006crystalstructuresof pages 5-7).
4. Substrate Specificity  
   The substrate specificity of IRAK2, although not exhaustively defined in the literature, is inferred by its close relationship with other members of the IRAK family. IRAK2 phosphorylates target proteins involved in the propagation of immune and inflammatory signals through pathways such as NF‑κB activation and stress‑kinase stimulation (benosman2013interleukin1receptorassociatedkinase2 pages 1-3). The precise consensus substrate motif for IRAK2 has not been conclusively determined; however, substrates of related serine/threonine kinases often contain sequences that display a preference for basic residues in proximity to the phosphorylation site. For example, many kinases of this group have been reported to recognize motifs such as an RxRxxp[ST] pattern, where “p[ST]” represents the phosphorylated serine or threonine. On the basis of such comparisons, IRAK2 is hypothesized to target serine or threonine residues positioned in contexts that potentially include basic amino acids. The functional consequence of such phosphorylation events is the modulation of downstream signaling cascades that lead to pro‑inflammatory gene transcription and mRNA stabilization through the activation of transcription factors like NF‑κB and stress‑responsive kinases such as JNK and p38 MAPK (benosman2013interleukin1receptorassociatedkinase2 pages 1-3, gosu2012molecularevolutionand pages 1-2).
5. Structure  
   The three‑dimensional organization of IRAK2 is defined by its modular domain architecture, which underpins its role in both catalytic functions and the assembly of multi‑protein complexes. At the N‑terminus, IRAK2 contains a death domain (DD) that is critical for mediating homotypic interactions with adaptor proteins such as MyD88. This domain is indispensable for the recruitment of IRAK2 to the IL‑1 receptor complex, where it contributes to the formation of the Myddosome—a multiprotein signaling complex that orchestrates downstream activation of NF‑κB and MAP kinases (maschera1999overexpressionofan pages 4-5, benosman2013interleukin1receptorassociatedkinase2 pages 1-3). Centrally located is the kinase domain, which is organized into the typical two‑lobe structure observed in serine/threonine kinases. The N‑terminal lobe of the kinase domain houses the ATP‑binding pocket and beta‑sheet structure, whereas the C‑terminal lobe contains the catalytic loop, the activation segment (T‑loop), and regions that contribute to substrate orientation. Conserved features in this domain include a catalytic lysine residue that is essential for ATP binding and a C‑helix that plays a role in stabilizing the active conformation of the kinase. Although there are reports indicating that some isoforms of IRAK2 may exhibit attenuated catalytic activity due to substitutions at key catalytic residues, structural modeling based on closely related kinases (such as IRAK4) supports that the overall fold is maintained. In addition to the core kinase domain, C‑terminal regions of IRAK2 contribute to substrate recruitment and mediate interactions necessary for the formation of higher‑order signaling assemblies. Unique structural features include the juxtaposition of the death domain and the kinase domain, which allows IRAK2 to function both as an enzymatic mediator and as a scaffolding protein in the propagation and regulation of inflammatory signals (dardick2006plantandanimal pages 6-7, gosu2012molecularevolutionand pages 14-15, klausheisen2011structurefunctionsimilaritiesbetween pages 1-2).
6. Regulation  
   The regulation of IRAK2 involves a multifaceted network of post‑translational modifications and protein–protein interactions that modulate its activity in response to IL‑1 receptor engagement. Following the binding of IL‑1 to its receptor, IRAK2 is recruited to the receptor complex through its death domain, where it becomes a part of the Myddosome along with MyD88 and IRAK4. An essential regulatory event is the phosphorylation of IRAK2; this modification, mediated by upstream kinases such as IRAK4, is critical for promoting conformational changes within IRAK2 that enable its proper function within the signaling complex (benosman2013interleukin1receptorassociatedkinase2 pages 1-3, gosu2012molecularevolutionand pages 14-15). The phosphorylation status of IRAK2 influences its ability to activate downstream effector kinases—including those responsible for triggering the NF‑κB pathway—and consequently controls the amplitude and duration of the inflammatory response.  
   In addition to phosphorylation, alternative splicing of the IRAK2 mRNA results in the production of different isoforms that may have distinct regulatory properties and capacities to propagate signal transduction. Some splice variants are linked to enhanced pro‑inflammatory activity, while others can modulate processes such as endoplasmic reticulum stress‑induced apoptosis through their influence on transcription factors like CHOP (biswas2007myeloiddifferentiationfactor pages 4-5, smith2011irak2regulatesil1mediated pages 9-9). Furthermore, the incorporation of IRAK2 into the Myddosome via interactions mediated by its death domain ensures spatial and temporal control of its signaling function. Such regulated assembly is critical for enabling rapid responses to pathogen‑associated signals while preventing excessive or prolonged activation that might lead to pathological inflammation (benosman2013interleukin1receptorassociatedkinase2 pages 1-3, gosu2012molecularevolutionand pages 14-15).
7. Function  
   Within the IL‑1 receptor and Toll‑like receptor signaling pathways, IRAK2 serves as a pivotal mediator that bridges receptor activation to downstream effector responses. Upon binding of IL‑1 to its receptor, IRAK2 is swiftly recruited to the receptor complex by its N‑terminal death domain, which drives the assembly of the Myddosome together with adapter proteins and other IRAK family members such as IRAK1 and IRAK4. This assembly is fundamental for eliciting the activation of NF‑κB, a transcription factor central to the induction of pro‑inflammatory genes. In essence, IRAK2 facilitates the phosphorylation cascade that culminates in the degradation of inhibitors of NF‑κB and the subsequent nuclear translocation of the transcription factor. In parallel, IRAK2 contributes to the activation of MAP kinase signaling pathways, including those mediated by JNK and p38 MAPK. These kinases are involved in the regulation of additional transcription factors and in the post‑transcriptional stabilization of mRNAs encoding cytokines and other inflammatory mediators (benosman2013interleukin1receptorassociatedkinase2 pages 1-3, chaudhary2015recentadvancesin pages 12-13).  
   Beyond classical inflammatory signaling, IRAK2 has been implicated in additional cellular processes such as the response to endoplasmic reticulum stress, where its modulation of apoptotic signaling through the transcription factor CHOP links inflammatory pathways to programmed cell death. Expression of IRAK2 is observed in various cell types that participate in innate immunity, and its ability to regulate both transcriptional and post‑transcriptional events places it at a central hub in inflammatory signal transduction. Through its participation in multiple signaling cascades, IRAK2 not only promotes the rapid activation of pro‑inflammatory pathways but also contributes to the fine‑tuning of immune responses by modulating cytokine production and mRNA stabilization (biswas2007myeloiddifferentiationfactor pages 4-5, chaudhary2015recentadvancesin pages 12-13).
8. Other Comments  
   In addition to its central role in IL‑1 and Toll‑like receptor signal transduction, IRAK2 has been linked to the regulation of endoplasmic reticulum stress responses in cellular models. Experimental evidence from studies employing shRNA‑mediated knockdown and genetic knockout models indicates that modulation of IRAK2 levels can influence the induction of pro‑apoptotic transcription factors such as CHOP, thereby connecting inflammatory signaling with apoptotic pathways (smith2011irak2regulatesil1mediated pages 9-9). Furthermore, genetic variation in IRAK2 has been associated with differences in cytokine production, including an increased IL‑1‑induced IL‑17 output observed in certain mouse strains that express specific IRAK2 isoforms. Such findings underscore the potential involvement of IRAK2 in the development of pathogenic Th17 responses and its broader implications in autoimmune and inflammatory diseases. Owing to its critical position in orchestrating NF‑κB activation, mRNA stabilization of inflammatory mediators, and apoptotic responses in the context of endoplasmic reticulum stress, IRAK2 is being increasingly recognized as a potential therapeutic target. Although selective chemical inhibitors specific for IRAK2 are not as well established as those for IRAK1 or IRAK4, ongoing drug discovery efforts are aimed at modulating the activity of IRAK family members to achieve controlled suppression of pathological inflammation (winkler2021theinterleukin‐1receptor–associated pages 1-4, patra2016recentprogressin pages 13-15).
9. References  
   benosman2013interleukin1receptorassociatedkinase2 pages 1-3; benosman2013interleukin1receptorassociatedkinase2 pages 3-3; biswas2007myeloiddifferentiationfactor pages 4-5; chaudhary2015recentadvancesin pages 12-13; dardick2006plantandanimal pages 6-7; gosu2012molecularevolutionand pages 1-2; gosu2012molecularevolutionand pages 14-15; maschera1999overexpressionofan pages 4-5; wang2006crystalstructuresof pages 5-7; smith2011irak2regulatesil1mediated pages 9-9; kim2024recentadvancesin pages 1-3; kim2024recentadvancesin pages 12-14; klausheisen2011structurefunctionsimilaritiesbetween pages 1-2; patra2016recentprogressin pages 8-10; patra2016recentprogressin pages 12-13; patra2016recentprogressin pages 13-15; gottipati2008irak1acritical pages 3-5; gottipati2008irak1acritical pages 5-6; winkler2021theinterleukin‐1receptor–associated pages 1-4.

References

1. (benosman2013interleukin1receptorassociatedkinase2 pages 1-3): Samir Benosman, Palaniyandi Ravanan, Ricardo G. Correa, Ying-Chen Hou, Minjia Yu, Muhammet Fatih Gulen, Xiaoxia Li, James Thomas, Michael Cuddy, Yasuko Matsuzawa, Renata Sano, Paul Diaz, Shu-ichi Matsuzawa, and John C. Reed. Interleukin-1 receptor-associated kinase-2 (irak2) is a critical mediator of endoplasmic reticulum (er) stress signaling. PLoS ONE, 8:e64256, May 2013. URL: https://doi.org/10.1371/journal.pone.0064256, doi:10.1371/journal.pone.0064256. This article has 40 citations and is from a peer-reviewed journal.
2. (benosman2013interleukin1receptorassociatedkinase2 pages 3-3): Samir Benosman, Palaniyandi Ravanan, Ricardo G. Correa, Ying-Chen Hou, Minjia Yu, Muhammet Fatih Gulen, Xiaoxia Li, James Thomas, Michael Cuddy, Yasuko Matsuzawa, Renata Sano, Paul Diaz, Shu-ichi Matsuzawa, and John C. Reed. Interleukin-1 receptor-associated kinase-2 (irak2) is a critical mediator of endoplasmic reticulum (er) stress signaling. PLoS ONE, 8:e64256, May 2013. URL: https://doi.org/10.1371/journal.pone.0064256, doi:10.1371/journal.pone.0064256. This article has 40 citations and is from a peer-reviewed journal.
3. (biswas2007myeloiddifferentiationfactor pages 4-5): Subhra K. Biswas and Vinay Tergaonkar. Myeloid differentiation factor 88-independent toll-like receptor pathway: sustaining inflammation or promoting tolerance? The International Journal of Biochemistry & Cell Biology, 39:1582-1592, Jan 2007. URL: https://doi.org/10.1016/j.biocel.2007.04.021, doi:10.1016/j.biocel.2007.04.021. This article has 97 citations.
4. (chaudhary2015recentadvancesin pages 12-13): Divya Chaudhary, Shaughnessy Robinson, and Donna L. Romero. Recent advances in the discovery of small molecule inhibitors of interleukin-1 receptor-associated kinase 4 (irak4) as a therapeutic target for inflammation and oncology disorders. Journal of medicinal chemistry, 58 1:96-110, Jan 2015. URL: https://doi.org/10.1021/jm5016044, doi:10.1021/jm5016044. This article has 114 citations and is from a highest quality peer-reviewed journal.
5. (dardick2006plantandanimal pages 6-7): 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 325 citations and is from a highest quality peer-reviewed journal.
6. (gosu2012molecularevolutionand pages 1-2): Vijayakumar Gosu, Shaherin Basith, Prasannavenkatesh Durai, and Sangdun Choi. Molecular evolution and structural features of irak family members. PLoS ONE, 7:e49771, Nov 2012. URL: https://doi.org/10.1371/journal.pone.0049771, doi:10.1371/journal.pone.0049771. This article has 64 citations and is from a peer-reviewed journal.
7. (gosu2012molecularevolutionand pages 14-15): Vijayakumar Gosu, Shaherin Basith, Prasannavenkatesh Durai, and Sangdun Choi. Molecular evolution and structural features of irak family members. PLoS ONE, 7:e49771, Nov 2012. URL: https://doi.org/10.1371/journal.pone.0049771, doi:10.1371/journal.pone.0049771. This article has 64 citations and is from a peer-reviewed journal.
8. (maschera1999overexpressionofan pages 4-5): Barbara MASCHERA, Keith RAY, Kimberly BURNS, and Filippo VOLPE. Overexpression of an enzymically inactive interleukin-1-receptor-associated kinase activates nuclear factor-κb. Biochemical Journal, 339:227-231, Apr 1999. URL: https://doi.org/10.1042/bj3390227, doi:10.1042/bj3390227. This article has 119 citations and is from a domain leading peer-reviewed journal.
9. (wang2006crystalstructuresof pages 5-7): Zhulun Wang, Jinsong Liu, Athena Sudom, Merrill Ayres, Shyun Li, Holger Wesche, Jay P. Powers, and Nigel P.C. Walker. Crystal structures of irak-4 kinase in complex with inhibitors: a serine/threonine kinase with tyrosine as a gatekeeper. Structure, 14:1835-1844, Dec 2006. URL: https://doi.org/10.1016/j.str.2006.11.001, doi:10.1016/j.str.2006.11.001. This article has 187 citations and is from a domain leading peer-reviewed journal.
10. (kim2024recentadvancesin pages 1-3): Kyeong Min Kim, Na-Hee Hwang, Ja-Shil Hyun, and Dongyun Shin. Recent advances in irak1: pharmacological and therapeutic aspects. Molecules, 29:2226, May 2024. URL: https://doi.org/10.3390/molecules29102226, doi:10.3390/molecules29102226. This article has 7 citations and is from a peer-reviewed journal.
11. (smith2011irak2regulatesil1mediated pages 9-9): Patrick M. Smith, Berri Jacque, James R. Conner, Alexander Poltorak, and Miguel J. Stadecker. Irak-2 regulates il-1-mediated pathogenic th17 cell development in helminthic infection. PLoS Pathogens, 7:e1002272, Oct 2011. URL: https://doi.org/10.1371/journal.ppat.1002272, doi:10.1371/journal.ppat.1002272. This article has 22 citations and is from a highest quality peer-reviewed journal.
12. (gottipati2008irak1acritical pages 3-5): Sridevi Gottipati, Navin L. Rao, and Wai-Ping Fung-Leung. Irak1: a critical signaling mediator of innate immunity. Cellular Signalling, 20:269-276, Feb 2008. URL: https://doi.org/10.1016/j.cellsig.2007.08.009, doi:10.1016/j.cellsig.2007.08.009. This article has 312 citations and is from a peer-reviewed journal.
13. (gottipati2008irak1acritical pages 5-6): Sridevi Gottipati, Navin L. Rao, and Wai-Ping Fung-Leung. Irak1: a critical signaling mediator of innate immunity. Cellular Signalling, 20:269-276, Feb 2008. URL: https://doi.org/10.1016/j.cellsig.2007.08.009, doi:10.1016/j.cellsig.2007.08.009. This article has 312 citations and is from a peer-reviewed journal.
14. (kim2024recentadvancesin pages 12-14): Kyeong Min Kim, Na-Hee Hwang, Ja-Shil Hyun, and Dongyun Shin. Recent advances in irak1: pharmacological and therapeutic aspects. Molecules, 29:2226, May 2024. URL: https://doi.org/10.3390/molecules29102226, doi:10.3390/molecules29102226. This article has 7 citations and is from a peer-reviewed journal.
15. (winkler2021theinterleukin‐1receptor–associated pages 1-4): Aaron Winkler, Weiyong Sun, Saurav De, Aiping Jiao, M. Nusrat Sharif, Peter T. Symanowicz, Shruti Athale, Julia H. Shin, Ju Wang, Bruce A. Jacobson, Simeon J. Ramsey, Ken Dower, Tatyana Andreyeva, Heng Liu, Martin Hegen, Bruce L. Homer, Joanne Brodfuehrer, Mera Tilley, Steven A. Gilbert, Spencer I. Danto, Jean J. Beebe, Betsy J. Barnes, Virginia Pascual, Lih‐Ling Lin, Iain Kilty, Margaret Fleming, and Vikram R. Rao. The interleukin‐1 receptor–associated kinase 4 inhibitor pf‐06650833 blocks inflammation in preclinical models of rheumatic disease and in humans enrolled in a randomized clinical trial. Arthritis & Rheumatology, 73:2206-2218, Nov 2021. URL: https://doi.org/10.1002/art.41953, doi:10.1002/art.41953. This article has 65 citations.
16. (klausheisen2011structurefunctionsimilaritiesbetween pages 1-2): Dörte Klaus-Heisen, Alessandra Nurisso, Anna Pietraszewska-Bogiel, Malick Mbengue, Sylvie Camut, Ton Timmers, Carole Pichereaux, Michel Rossignol, Theodorus W.J. Gadella, Anne Imberty, Benoit Lefebvre, and Julie V. Cullimore. Structure-function similarities between a plant receptor-like kinase and the human interleukin-1 receptor-associated kinase-4. Journal of Biological Chemistry, 286:11202-11210, Apr 2011. URL: https://doi.org/10.1074/jbc.m110.186171, doi:10.1074/jbc.m110.186171. This article has 78 citations and is from a domain leading peer-reviewed journal.
17. (patra2016recentprogressin pages 12-13): Mahesh Patra and Sangdun Choi. Recent progress in the molecular recognition and therapeutic importance of interleukin-1 receptor-associated kinase 4. Molecules, 21:1529, Nov 2016. URL: https://doi.org/10.3390/molecules21111529, doi:10.3390/molecules21111529. This article has 43 citations and is from a peer-reviewed journal.
18. (patra2016recentprogressin pages 13-15): Mahesh Patra and Sangdun Choi. Recent progress in the molecular recognition and therapeutic importance of interleukin-1 receptor-associated kinase 4. Molecules, 21:1529, Nov 2016. URL: https://doi.org/10.3390/molecules21111529, doi:10.3390/molecules21111529. This article has 43 citations and is from a peer-reviewed journal.
19. (patra2016recentprogressin pages 8-10): Mahesh Patra and Sangdun Choi. Recent progress in the molecular recognition and therapeutic importance of interleukin-1 receptor-associated kinase 4. Molecules, 21:1529, Nov 2016. URL: https://doi.org/10.3390/molecules21111529, doi:10.3390/molecules21111529. This article has 43 citations and is from a peer-reviewed journal.