1. Phylogeny  
   IRR (Insulin Receptor‐Related Receptor) is a member of the insulin receptor family, which also comprises the insulin receptor (IR) and the insulin‐like growth factor 1 receptor (IGF‐1R). Orthologs of IRR have been identified in a wide range of vertebrate species, from amphibians to humans, which indicates that the protein is evolutionarily conserved across species (deyev2013structuraldeterminantsof pages 1-2, korotkova2022insulinreceptorrelatedreceptor pages 1-2). Within the kinome, IRR is assigned to the receptor tyrosine kinase (RTK) superfamily and more specifically to the insulin receptor subgroup where the extracellular domain architecture, consisting of leucine-rich repeats, a cysteine-rich region, and fibronectin type III repeats, is a conserved characteristic element (deyev2013structuraldeterminantsof pages 1-2, bershatsky2023diversityofstructural pages 1-2). Its evolutionary trajectory is marked by significant divergence in ligand responsiveness; while the ancestral receptor appears to have given rise to members that interact with peptide hormones such as insulin or IGF‐1, IRR has specialized as a pH sensor, being activated by increases in extracellular alkalinity. This divergence is also evident in the overall glycosylation pattern and structural differences in the domains that mediate ligand binding and receptor activation (deyev2017sitedirectedmutagenesisof pages 1-3).
2. Reaction Catalyzed  
   IRR catalyzes an ATP-dependent phosphorylation reaction typical of receptor tyrosine kinases. In this reaction, ATP serves as a phosphate donor to specific tyrosine residues on substrate proteins. The overall reaction can be summarized as follows: ATP + [protein]–tyrosine → ADP + [protein]–phosphotyrosine + H⁺. This autophosphorylation reaction, which also extends to the phosphorylation of intracellular substrates such as IRS proteins, is central to the protein’s signal transduction function (white1994theinsulinsignaling pages 1-1, adams2000structureandfunction pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of IRR, like that of other receptor tyrosine kinases, depends on the presence of divalent metal ions. In particular, Mg²⁺ is required as a cofactor to coordinate the binding of ATP and to facilitate the transfer of the phosphate group during the phosphorylation reaction (adams2000structureandfunction pages 5-7).
4. Substrate Specificity  
   IRR preferentially phosphorylates tyrosine residues on substrate proteins. While no single consensus motif has been exhaustively defined for IRR, the enzyme is known to target intracellular substrates such as insulin receptor substrate‐1 (IRS‐1) and IRS‐2. The substrate specificity is consistent with that observed for other members of the insulin receptor family, which recognize and phosphorylate tyrosine‐containing motifs that serve as docking sites for downstream signaling molecules. The specificity for tyrosine residues in these substrates underpins the initiation of signaling cascades that regulate metabolic functions (hirayama1999insulinreceptorrelatedreceptor pages 3-4, deyev2013structuraldeterminantsof pages 1-2).
5. Structure  
   IRR is a modular protein that features a multi‐domain organization characteristic of the insulin receptor family. Its structure comprises an N‐terminal signal peptide followed by an extracellular region that includes two leucine‐rich repeat domains (L1 and L2), a cysteine‐rich (CR) domain, and three fibronectin type III (FnIII) repeats. The extracellular region is responsible for ligand (or, in the case of IRR, pH) sensing and mediates conformational changes upon activation. IRR exists as a preformed disulfide‐bonded dimer, forming an (αβ)₂ heterotetramer. The extracellular domain has been observed in a “Λ‐shaped” conformation at neutral pH, which shifts to a symmetric “T‐shaped” active dimer when exposed to alkaline pH conditions (deyev2013structuraldeterminantsof pages 1-2, wang2023structuralbasisof pages 3-4). Key structural determinants of pH responsiveness reside within the L1C region; residues such as Leu‐135, Gly‐188, Arg‐244, His‐318, and Lys‐319 contribute cooperatively to the activation process. In addition, mutagenesis studies have identified a role for a residue in the fibronectin region (e.g., T582 in FnIII‐1), which is critical for the receptor’s pH‐sensing capability (deyev2013structuraldeterminantsof pages 9-10, deyev2017sitedirectedmutagenesisof pages 1-3). The intracellular portion of IRR encompasses a single transmembrane helix and a cytoplasmic tyrosine kinase domain that contains characteristic structural features such as an activation loop, a C-helix, and a hydrophobic spine that are essential for catalytic activity and regulation (deyev2017sitedirectedmutagenesisof pages 7-10, wang2023structuralbasisof pages 4-6).
6. Regulation  
   The activation of IRR is uniquely regulated by the extracellular pH environment rather than by direct binding of a polypeptide ligand. Under neutral conditions, IRR remains in an auto-inhibited conformation; however, when the extracellular pH shifts to alkaline values, key electrostatic interactions within the extracellular domain are disrupted. This leads to a scissor-like rotation at the dimer interface and the transition from a “Λ‐shaped” inactive conformation to a “T‐shaped” active state in which the intracellular kinase domains are brought into proximity, allowing for trans‐autophosphorylation (wang2023structuralbasisof pages 3-4, deyev2013structuraldeterminantsof pages 1-2). The mechanism of regulation involves pH‐induced deprotonation of basic residues and destabilization of salt bridges at the interface of the L1 and FnIII‐2 domains. Additionally, the degree of glycosylation of the extracellular domains affects receptor activation; IRR is less glycosylated compared to IR, a characteristic that facilitates the necessary conformational changes for pH sensing (deyev2017sitedirectedmutagenesisof pages 3-7, wang2023structuralbasisof pages 4-6). The regulation mediated by extracellular alkalinity is distinct from the ligand‐induced mechanisms observed in other receptor tyrosine kinases (hirayama1999insulinreceptorrelatedreceptor pages 3-4).
7. Function  
   IRR functions primarily as an extracellular pH sensor. It is activated by increases in the extracellular pH, a property that distinguishes it from other members of the insulin receptor family that are activated by insulin or IGF. Once activated under alkaline conditions, IRR undergoes autophosphorylation and subsequently phosphorylates intracellular substrates, most notably IRS‐1 and IRS‐2. This phosphorylation cascade ultimately leads to the activation of downstream signaling pathways, including the kinase AKT1/PKB, which play roles in regulating cellular metabolism. Expression studies have shown that IRR is predominantly expressed in tissues that are exposed to variable pH conditions, such as kidney cells involved in bicarbonate secretion, pancreatic cells, and certain cells in the stomach (deyev2013structuraldeterminantsof pages 1-2, kitamura2001preservedpancreaticβcell pages 5-7, korotkova2022insulinreceptorrelatedreceptor pages 1-2). In experimental models, knockout mice for IRR show impaired responses to alkaline challenges, consistent with a role in acid–base homeostasis. The downstream signaling mediated by IRR and its substrates implicates it in the regulation of metabolic pathways similar to those driven by insulin signaling, yet its activation mechanism remains solely pH-dependent (deyev2013structuraldeterminantsof pages 1-2, wang2023structuralbasisof pages 1-3).
8. Other Comments  
   IRR is classified as an orphan receptor because no endogenous peptide or protein ligand has been identified; its activation is entirely dependent on the extracellular pH. Due to this unique mode of activation, specific inhibitors targeting IRR’s ligand-binding function are not available, and research has instead focused on its pH‐dependent conformational regulation. Although IRR plays an established role in pH sensing and acid–base balance, its involvement in other physiological or pathological processes remains under investigation. Its close structural relationship to the insulin receptor hints at potential crosstalk or compensatory signaling in metabolic regulation; however, the absence of a classical ligand differentiates its function from that of IR and IGF‐1R (meyts2004insulinandits pages 4-5, garzagarcia2007rilmaweb‐based pages 1-2, ward2009ligand‐inducedactivationof pages 1-2).
9. References  
   deyev2013structuraldeterminantsof pages 1-2  
   deyev2013structuraldeterminantsof pages 9-10  
   deyev2017sitedirectedmutagenesisof pages 1-3  
   deyev2017sitedirectedmutagenesisof pages 7-10  
   hirayama1999insulinreceptorrelatedreceptor pages 3-4  
   kitamura2001preservedpancreaticβcell pages 5-7  
   wang2023structuralbasisof pages 3-4  
   wang2023structuralbasisof pages 4-6  
   korotkova2022insulinreceptorrelatedreceptor pages 1-2  
   meyts2004insulinandits pages 4-5  
   garzagarcia2007rilmaweb‐based pages 1-2  
   ward2009ligand‐inducedactivationof pages 1-2

References

1. (deyev2013structuraldeterminantsof pages 1-2): Igor E. Deyev, Alla V. Mitrofanova, Egor S. Zhevlenev, Nikita Radionov, Anastasiya A. Berchatova, Nadezhda V. Popova, Oxana V. Serova, and Alexander G. Petrenko. Structural determinants of the insulin receptor-related receptor activation by alkali. Journal of Biological Chemistry, 288:33884-33893, Nov 2013. URL: https://doi.org/10.1074/jbc.m113.483172, doi:10.1074/jbc.m113.483172. This article has 38 citations and is from a domain leading peer-reviewed journal.
2. (deyev2013structuraldeterminantsof pages 9-10): Igor E. Deyev, Alla V. Mitrofanova, Egor S. Zhevlenev, Nikita Radionov, Anastasiya A. Berchatova, Nadezhda V. Popova, Oxana V. Serova, and Alexander G. Petrenko. Structural determinants of the insulin receptor-related receptor activation by alkali. Journal of Biological Chemistry, 288:33884-33893, Nov 2013. URL: https://doi.org/10.1074/jbc.m113.483172, doi:10.1074/jbc.m113.483172. This article has 38 citations and is from a domain leading peer-reviewed journal.
3. (deyev2017sitedirectedmutagenesisof pages 1-3): Igor Deyev, Natalia Chachina, Egor Zhevlenev, and Alexander Petrenko. Site-directed mutagenesis of the fibronectin domains in insulin receptor-related receptor. International Journal of Molecular Sciences, 18:2461, Nov 2017. URL: https://doi.org/10.3390/ijms18112461, doi:10.3390/ijms18112461. This article has 6 citations and is from a peer-reviewed journal.
4. (deyev2017sitedirectedmutagenesisof pages 3-7): Igor Deyev, Natalia Chachina, Egor Zhevlenev, and Alexander Petrenko. Site-directed mutagenesis of the fibronectin domains in insulin receptor-related receptor. International Journal of Molecular Sciences, 18:2461, Nov 2017. URL: https://doi.org/10.3390/ijms18112461, doi:10.3390/ijms18112461. This article has 6 citations and is from a peer-reviewed journal.
5. (deyev2017sitedirectedmutagenesisof pages 7-10): Igor Deyev, Natalia Chachina, Egor Zhevlenev, and Alexander Petrenko. Site-directed mutagenesis of the fibronectin domains in insulin receptor-related receptor. International Journal of Molecular Sciences, 18:2461, Nov 2017. URL: https://doi.org/10.3390/ijms18112461, doi:10.3390/ijms18112461. This article has 6 citations and is from a peer-reviewed journal.
6. (hirayama1999insulinreceptorrelatedreceptor pages 3-4): I. Hirayama, H. Tamemoto, H. Yokota, S. Kubo, J. Wang, H. Kuwano, Y. Nagamachi, T. Takeuchi, and T. Izumi. Insulin receptor-related receptor is expressed in pancreatic beta-cells and stimulates tyrosine phosphorylation of insulin receptor substrate-1 and -2. Diabetes, 48:1237-1244, Jun 1999. URL: https://doi.org/10.2337/diabetes.48.6.1237, doi:10.2337/diabetes.48.6.1237. This article has 72 citations.
7. (kitamura2001preservedpancreaticβcell pages 5-7): Tadahiro Kitamura, Yoshiaki Kido, Serge Nef, Jussi Merenmies, Luis F. Parada, and Domenico Accili. Preserved pancreatic β-cell development and function in mice lacking the insulin receptor-related receptor. Molecular and Cellular Biology, 21:5624-5630, Aug 2001. URL: https://doi.org/10.1128/mcb.21.16.5624-5630.2001, doi:10.1128/mcb.21.16.5624-5630.2001. This article has 132 citations and is from a domain leading peer-reviewed journal.
8. (meyts2004insulinandits pages 4-5): Pierre De Meyts. Insulin and its receptor: structure, function and evolution. BioEssays : news and reviews in molecular, cellular and developmental biology, 26 12:1351-62, Dec 2004. URL: https://doi.org/10.1002/bies.20151, doi:10.1002/bies.20151. This article has 468 citations.
9. (wang2023structuralbasisof pages 1-3): Liwei Wang, Catherin Hall, Jie Li, E. Choi, and X. Bai. Structural basis of the alkaline ph-dependent activation of insulin receptor-related receptor. Nature Structural & Molecular Biology, 30:661-669, Apr 2023. URL: https://doi.org/10.1038/s41594-023-00974-0, doi:10.1038/s41594-023-00974-0. This article has 13 citations.
10. (adams2000structureandfunction pages 5-7): T. E. Adams, V. C. Epa, T. P. J. Garrett, and C. W. Ward\*. Structure and function of the type 1 insulin-like growth factor receptor. Cellular and Molecular Life Sciences, 57:1050-1093, Jul 2000. URL: https://doi.org/10.1007/pl00000744, doi:10.1007/pl00000744. This article has 869 citations and is from a domain leading peer-reviewed journal.
11. (bershatsky2023diversityofstructural pages 1-2): Yaroslav V. Bershatsky, Andrey S. Kuznetsov, Aisha R. Idiatullina, Olga V. Bocharova, Sofya M. Dolotova, Alina A. Gavrilenkova, Oxana V. Serova, Igor E. Deyev, Tatiana V. Rakitina, Olga T. Zangieva, Konstantin V. Pavlov, Oleg V. Batishchev, Vladimir V. Britikov, Sergey A. Usanov, Alexander S. Arseniev, Roman G. Efremov, and Eduard V. Bocharov. Diversity of structural, dynamic, and environmental effects explain a distinctive functional role of transmembrane domains in the insulin receptor subfamily. International Journal of Molecular Sciences, 24:3906, Feb 2023. URL: https://doi.org/10.3390/ijms24043906, doi:10.3390/ijms24043906. This article has 4 citations and is from a peer-reviewed journal.
12. (garzagarcia2007rilmaweb‐based pages 1-2): Acely Garza-Garcia, Dhaval S. Patel, David Gems, and Paul C. Driscoll. Rilm: a web‐based resource to aid comparative and functional analysis of the insulin and igf‐1 receptor family. Human Mutation, Jul 2007. URL: https://doi.org/10.1002/humu.20491, doi:10.1002/humu.20491. This article has 19 citations and is from a domain leading peer-reviewed journal.
13. (korotkova2022insulinreceptorrelatedreceptor pages 1-2): Daria D. Korotkova, Elena A. Gantsova, Alexander S. Goryashchenko, Fedor M. Eroshkin, Oxana V. Serova, Alexey S. Sokolov, Fedor Sharko, Svetlana V. Zhenilo, Natalia Y. Martynova, Alexander G. Petrenko, Andrey G. Zaraisky, and Igor E. Deyev. Insulin receptor-related receptor regulates the rate of early development in xenopus laevis. International Journal of Molecular Sciences, 23:9250, Aug 2022. URL: https://doi.org/10.3390/ijms23169250, doi:10.3390/ijms23169250. This article has 7 citations and is from a peer-reviewed journal.
14. (wang2023structuralbasisof pages 3-4): Liwei Wang, Catherin Hall, Jie Li, E. Choi, and X. Bai. Structural basis of the alkaline ph-dependent activation of insulin receptor-related receptor. Nature Structural & Molecular Biology, 30:661-669, Apr 2023. URL: https://doi.org/10.1038/s41594-023-00974-0, doi:10.1038/s41594-023-00974-0. This article has 13 citations.
15. (wang2023structuralbasisof pages 4-6): Liwei Wang, Catherin Hall, Jie Li, E. Choi, and X. Bai. Structural basis of the alkaline ph-dependent activation of insulin receptor-related receptor. Nature Structural & Molecular Biology, 30:661-669, Apr 2023. URL: https://doi.org/10.1038/s41594-023-00974-0, doi:10.1038/s41594-023-00974-0. This article has 13 citations.
16. (ward2009ligand‐inducedactivationof pages 1-2): Colin W. Ward and Michael C. Lawrence. Ligand‐induced activation of the insulin receptor: a multi‐step process involving structural changes in both the ligand and the receptor. BioEssays, Apr 2009. URL: https://doi.org/10.1002/bies.200800210, doi:10.1002/bies.200800210. This article has 228 citations and is from a peer-reviewed journal.
17. (white1994theinsulinsignaling pages 1-1): MF White and CR Kahn. The insulin signaling system. The Journal of biological chemistry, 269 1:1-4, Jan 1994. URL: https://doi.org/10.1016/s0021-9258(17)42297-6, doi:10.1016/s0021-9258(17)42297-6. This article has 2126 citations.
18. (adams2000structureandfunction pages 1-2): T. E. Adams, V. C. Epa, T. P. J. Garrett, and C. W. Ward\*. Structure and function of the type 1 insulin-like growth factor receptor. Cellular and Molecular Life Sciences, 57:1050-1093, Jul 2000. URL: https://doi.org/10.1007/pl00000744, doi:10.1007/pl00000744. This article has 869 citations and is from a domain leading peer-reviewed journal.