

Key References

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Overview

The insulin receptor belongs to a subfamily of receptor tyrosine kinases that also includes the IGF-1 receptor and an orphan receptor called the insulin receptor-related receptor (IRR). It is a tetrameric protein consisting of two α - and two β -subunits encoded by the IR gene. The two subunits derived from a single chain proreceptor undergo post translational processing including cleavage by a furin-like enzyme and glycosylation forming a single α - β subunit complex. Two of the α - β dimers are then cross linked by disulfide bonds to form the tetramer.

Ligand binding (insulin or IGF-1) to the α -subunit leads to activation of the kinase activity in the β -subunit. Following this initial activation, phosphorylation of one β -subunit by the other (transphosphorylation), leads to a conformational change and a further increase in activity of the kinase domain. Activation of the tyrosine kinase domain leads to autophosphorylation of tyrosine residues in several regions of the intracellular β -subunit, including Tyr⁹⁶⁰ in the juxtamembrane region, creating an NPXpY recognition motif for the PTB domain of the IRS proteins, Tyr¹¹⁴⁶, Tyr¹¹⁵⁰ and Tyr¹¹⁵¹ in the regulatory loop and Tyr¹³¹⁶ and Tyr¹³²² in the C-terminus. The α - β heterodimers of the individual insulin, IGF-1 and the IRR receptors can form functional hybrids in which ligand binding to one receptor's binding site leads to activation of the other receptor in the heterodimer by this transphosphorylation process.

Intracellular substrates of the insulin and IGF-1 receptor tyrosine kinases that have been identified to date include insulin receptor substrate (IRS) proteins 1-4, Gab-1, p62^{dok}, Cbl, APS and the various isoforms of Shc. Following insulin stimulation, the

receptor directly phosphorylates most of these substrates on multiple tyrosine residues. These phosphorylated tyrosines occur in specific sequence motifs which once phosphorylated serve as 'docking sites' for intracellular molecules that contain the SH2 (Src-homology) domain, transmitting the insulin signal downstream. A few proteins that bind to phosphotyrosines in the IRS proteins do not contain known SH2 domains; these include the calcium ATPases SERCA 1 and 2, and the SV40 large T antigen. Negative regulation of insulin receptor signaling has been demonstrated by the tyrosine phosphatase PTP1B which dephosphorylates the phosphotyrosine residues in the insulin receptor kinase and also through direct association of the novel PIR domain of the Grb14 adaptor protein with the insulin receptor.

Alterations in the function of the insulin receptor, both genetic and acquired, can lead to several different disease states including insulin resistance, diabetes and growth retardation. Insulin resistance at the level of the receptor may be the result of genetic alterations in receptor expression or structure, secondary changes in receptor activity due to serine phosphorylation, or due to down-regulation of receptor concentration. Insulin resistance is also closely linked to other common health problems, including obesity, polycystic ovarian disease, hyperlipidemia, hypertension and atherosclerosis.

The insulin receptor is widely distributed throughout the body, found in tissues classically regarded as both insulin 'responsive' for example muscle, liver and fat and 'non-responsive' for example brain and the vascular system. It signals through two major signaling pathways, the IRS/PI 3-kinase pathway and the Ras-MAP kinase

pathway controlling processes including glucose transport, uptake and storage, glycogen synthesis, cell growth and differentiation, protein synthesis and gene expression.

Tissue specific knockouts of the insulin receptor have helped to define the role of the receptor in the classical insulin sensitive tissues and identified novel functions in other tissues. The Muscle specific Insulin Receptor Knockout (MIRKO) mouse model exhibits increased insulin stimulated glucose uptake in the fat suggesting 'cross-talk' between muscle and fat in insulin resistant states. Fat specific knockout (FIRKO) mice have decreased fat mass, are resistant to diet induced obesity and have an extended lifespan suggesting an interesting role for the insulin receptor in regulating longevity. The neuron specific insulin receptor knockout (NIRKO) has confirmed the importance of the receptor in brain and highlighted a role for it in appetite regulation.

Defining the key steps that lead to specificity in insulin signaling should offer new therapeutic approaches for patients suffering from insulin resistant states, including type 2 diabetes.

FAMILY MEMBERS	Insulin receptor	Insulin-like growth factor I receptor	IRR
OTHER NAMES	Insr, IR	IGFR1, JTK13, Somatomedin receptor	INSRR, Insulin receptor-related receptor, IR-related receptor, IRRR
MOLECULAR WEIGHT/ STRUCTURAL DATA	α -subunit: 135 kDa, 719 aa, β -subunit: 95 kDa, 620 aa	154 kDa, 1367 aa	143 kDa, 1297 aa
ISOFORMS	Not found	IGF1Ra, IGF1Rb	Not known
SPECIES	Mammals, fish, <i>C. Elegans</i> , <i>Xenopus</i>	Human, bovine, mouse, pig, rat	Human, mouse, rat, guinea pig
DOMAIN ORGANIZATION	Tetramer of 2 α and 2 β subunits, β -chain contains kinase domains, 2 fibronectin type III-like domains	Tetramer of 2 α and 2 β chains, a chain contains ligand-binding domain, while the β chain contains kinase domain, 3 fibronectin, type-III domains	Probable tetramer of 2 α and 2 β chains, α chain contains ligand-binding domain, β chain contains kinase domain, 4 fibronectin type-III domains
PHOSPHORYLATION SITES	Tyr ¹¹⁴⁶ , Tyr ¹⁵⁰ , Tyr ¹¹⁵¹ , Ser ¹²⁷⁵ , Ser ¹³⁰⁹ , Tyr ⁹⁶⁰ , Tyr ¹³¹⁶ , Tyr ³²²	Tyr ¹¹⁶⁵	Tyr ¹¹⁴⁵
TISSUE DISTRIBUTION	Present in most tissues	Expressed in a variety of tissues	A subset of neuronal tissues, neuroblastomas, neural crest derived sensory and sympathetic neurons
SUBCELLULAR LOCALIZATION	Plasma membrane	Plasma membrane	Plasma membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	IRS1, IRS2, IRS3, IRS4, SHC, ADS, Sh2-B, Grb10, Grb7, CAP, p85 subunit of PI3K, SHPTP2 (Syp), SOCS1-3, PC-1	SOCS1-3, 14-3-3- $\epsilon/\beta/\zeta$, SHC, p85, IRS-1, IRS-2, IGF1R, JAK-1, PIK3R3, IGF-I, RACK1, PKCd, β -1 integrin, PKC μ , CSK, EHD1, NAG, ACP, AMP-PNP, Src	Not known
UPSTREAM ACTIVATORS	Insulin	IGF-I	Not known
DOWNSTREAM ACTIVATION	IRS1-4, Shc, PTP1B, cbl, p62 ^{dok}	IRS-1, IRS-2, Akt, and p42/44 MAPKs, PI3K	IRS-1, IRS-2, Ras
ACTIVATORS	Not known	Not known	Not known
SUBSTRATES	IRS 1-4, Gab-1, p62 ^{dok} , Cbl, APS, Shc	Not known	Not known
SELECTIVE INHIBITORS	Not known	Not known	Not known
NON-SELECTIVE INHIBITORS	(Hydroxy-2-naphthalenyl-methyl)phosphonic acid, quercetin (337951), staurosporine (S4400)	Not known	Not known

FOOTNOTES

InsR

SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Insulin signaling	Binds insulin-like growth factor I (IGF I) with a high affinity and IGF II with a lower affinity	Embryonal development of dorsal root and trigeminal neurons, development of sympathetic neurons, male sexual differentiation
DISEASE RELEVANCE	Type A syndrome of insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome, insulin resistance, type 2 diabetes	Gastrointestinal stromal tumors, Crohn's disease, primary breast cancer, prostate cancer, Graves' disease, pancreatic adenocarcinoma, thyroid carcinomas, colon cancer	Type-2 diabetes

FOOTNOTES