IRS1

Insulin receptor substrate 1 (IRS-1) is a signalling adapter protein that in humans is encoded by the *IRS-1* gene.[1] It contains a single pleckstrin homology (PH) domain at the N-terminus and a PTB domain ca. 40 residues downstream of this. Together with IRS2, IRS3 (pseudogene) and IRS4, it is homologous to the *Drosophila* protein *chico*, whose disruption extends the median lifespan of flies up to 48%.[2] Similarly, Irs1 mutant mice experience moderate life extension and delayed age-related pathologies.[3]

1 Function

Insulin receptor substrate 1 plays a key role in transmitting signals from the insulin and insulin-like growth factor-1 (IGF-1) receptors to intracellular pathways PI3K / Akt and Erk MAP kinase pathways.

Tyrosine phosphorylation of the insulin receptors or IGF-1 receptors, upon extracellular ligand binding, induces the cytoplasmic binding of IRS-1 to these receptors, through its PTB domains. Multiple tyrosine residues of IRS-1 itself are then phosphorylated by these receptors. This enables IRS-1 to activate several signalling pathways, including the PI3K pathway and the MAP kinase pathway.

IRS-1 plays important biological function for both metabolic and mitogenic (growth promoting) pathways: mice deficient of IRS1 have only a mild diabetic phenotype, but a pronounced growth impairment, i.e., IRS-1 knockout mice only reach 50% of the weight of normal mice. IRS-1 may also play a role in cancer, as it has been shown that transgenic mice overexpressing IRS-1 develop breast cancer.[4]

2 Regulation

The cellular protein levels of IRS-1 are regulated by the Cullin7 E3 ubiquitin ligase, which targets IRS-1 for ubiquitin mediated degradation by the proteasome.[5]

3 Interactions

IRS1 has been shown to interact with:

- Bcl-2,[6]
- Grb2,[7][8][9]
- INSR,[10][11]
- IGF1R,[12][13][14]
- JAK1,[15][16]
- JAK2,[15][17]
- MAPK8,[10][18]
- PIK3R1[8][19][20][21]
- PIK3R3,[22][23]
- PTK2,[24]
- PTPN11,[25][26]
- PTPN1,[27][28] and
- YWHAE.[29]

4 References

[1] Sun XJ, Rothenberg P, Kahn CR, Backer JM, Araki E, Wilden PA, Cahill DA, Goldstein BJ, White MF (Jul 1991). "Structure of the insulin receptor substrate IRS-1 defines a unique signal transduction protein". *Nature* **352** (6330): 73–7. doi:10.1038/352073a0. PMID 1648180.

[2] Clancy DJ, Gems D, Harshman LG, Oldham S, Stocker H, Hafen E, Leevers SJ, Partridge L (Apr 2001). "Extension of life-span by loss of CHICO, a Drosophila insulin receptor substrate protein". *Science* **292** (5514): 104–6. doi:10.1126/science.1057991. PMID 11292874.

[3] Selman C, Lingard S, Choudhury AI, Batterham RL, Claret M, Clements M, Ramadani F, Okkenhaug K, Schuster E, Blanc E, Piper MD, Al-Qassab H, Speakman JR, Carmignac D, Robinson IC, Thornton JM, Gems D, Partridge L, Withers DJ (Mar 2008). "Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice". *FASEB Journal* **22** (3): 807–18. doi:10.1096/fj.07-9261com. PMID 17928362.

[4] Dearth RK, Cui X, Kim HJ, Kuiatse I, Lawrence NA, Zhang X, Divisova J, Britton OL, Mohsin S, Allred DC, Hadsell DL, Lee AV (Dec 2006). "Mammary tumorigenesis and metastasis caused by overexpression of insulin receptor substrate 1 (IRS-1) or IRS-2". *Molecular and Cellular Biology* **26** (24): 9302–14. doi:10.1128/MCB.00260-06. PMC 1698542. PMID 17030631.

[5] Xu X, Sarikas A, Dias-Santagata DC, Dolios G, Lafontant PJ, Tsai SC, Zhu W, Nakajima H, Nakajima HO, Field LJ, Wang R, Pan ZQ (May 2008). "The CUL7 E3 ubiquitin ligase targets insulin receptor substrate 1 for ubiquitin-dependent degradation". *Molecular Cell* **30** (4): 403–14. doi:10.1016/j.molcel.2008.03.009. PMC 2633441. PMID 18498745.

[6] Ueno H, Kondo E, Yamamoto-Honda R, Tobe K, Nakamoto T, Sasaki K, Mitani K, Furusaka A, Tanaka T, Tsujimoto Y, Kadowaki T, Hirai H (Feb 2000). "Association of insulin receptor substrate proteins with Bcl-2 and their effects on its phosphorylation and anti-apoptotic function". *Molecular Biology of the Cell* **11** (2): 735–46. doi:10.1091/mbc.11.2.735. PMC 14806. PMID 10679027.

[7] Skolnik EY, Lee CH, Batzer A, Vicentini LM, Zhou M, Daly R, Myers MJ, Backer JM, Ullrich A, White MF (May 1993). "The SH2/SH3 domain-containing protein GRB2 interacts with tyrosine-phosphorylated IRS1 and Shc: implications for insulin control of ras signalling". *The EMBO Journal* **12** (5): 1929–36. PMC 413414. PMID 8491186.

[8] Morrison KB, Tognon CE, Garnett MJ, Deal C, Sorensen PH (Aug 2002). "ETV6-NTRK3 transformation requires insulin-like growth factor 1 receptor signaling and is associated with constitutive IRS-1 tyrosine phosphorylation". *Oncogene* **21** (37): 5684–95. doi:10.1038/sj.onc.1205669. PMID 12173038.

[9] Giorgetti-Peraldi S, Peyrade F, Baron V, Van Obberghen E (Dec 1995). "Involvement of Janus kinases in the insulin signaling pathway". *European Journal of Biochemistry / FEBS* **234** (2): 656–60. doi:10.1111/j.1432-1033.1995.656_b.x. PMID 8536716.

[10] Aguirre V, Werner ED, Giraud J, Lee YH, Shoelson SE, White MF (Jan 2002). "Phosphorylation of Ser307 in insulin receptor substrate-1 blocks interactions with the insulin receptor and inhibits insulin action". *The Journal of Biological Chemistry* **277** (2): 1531–7. doi:10.1074/jbc.M101521200. PMID 11606564.

[11] Sawka-Verhelle D, Tartare-Deckert S, White MF, Van Obberghen E (Mar 1996). "Insulin receptor substrate-2 binds to the insulin receptor through its phosphotyrosine-binding domain and through a newly identified domain comprising amino acids 591-786". *The Journal of Biological Chemistry* **271** (11): 5980–3. doi:10.1074/jbc.271.11.5980. PMID 8626379.

[12] Tartare-Deckert S, Sawka-Verhelle D, Murdaca J, Van Obberghen E (Oct 1995). "Evidence for a differential interaction of SHC and the insulin receptor substrate-1 (IRS-1) with the insulin-like growth factor-I (IGF-I) receptor in the yeast two-hybrid system". *The Journal of Biological Chemistry* **270** (40): 23456–60. doi:10.1074/jbc.270.40.23456. PMID 7559507.

[13] Dey BR, Frick K, Lopaczynski W, Nissley SP, Furlanetto RW (Jun 1996). "Evidence for the direct interaction of the insulin-like growth factor I receptor with IRS-1, Shc, and Grb10". *Molecular Endocrinology* **10** (6): 631–41. doi:10.1210/mend.10.6.8776723. PMID 8776723.

[14] Mañes S, Mira E, Gómez-Mouton C, Zhao ZJ, Lacalle RA, Martínez-A C (Apr 1999). "Concerted activity of tyrosine phosphatase SHP-2 and focal adhesion kinase in regulation of cell motility". *Molecular and Cellular Biology* **19** (4): 3125–35. doi:10.1128/mcb.19.4.3125. PMC 84106. PMID 10082579.

[15] Gual P, Baron V, Lequoy V, Van Obberghen E (Mar 1998). "Interaction of Janus kinases JAK-1 and JAK-2 with the insulin receptor and the insulin-like growth factor-1 receptor". *Endocrinology* **139** (3): 884–93. doi:10.1210/endo.139.3.5829. PMID 9492017.

[16] Johnston JA, Wang LM, Hanson EP, Sun XJ, White MF, Oakes SA, Pierce JH, O'Shea JJ (Dec 1995). "Interleukins 2, 4, 7, and 15 stimulate tyrosine phosphorylation of insulin receptor substrates 1 and 2 in T cells. Potential role of JAK kinases". *The Journal of Biological Chemistry* **270** (48): 28527–30. doi:10.1074/jbc.270.48.28527. PMID 7499365.

[17] Kawazoe Y, Naka T, Fujimoto M, Kohzaki H, Morita Y, Narazaki M, Okumura K, Saitoh H, Nakagawa R, Uchiyama Y, Akira S, Kishimoto T (Jan 2001). "Signal transducer and activator of transcription (STAT)-induced STAT inhibitor 1 (SSI-1)/suppressor of cytokine signaling 1 (SOCS1) inhibits insulin signal transduction pathway through modulating insulin receptor substrate 1 (IRS-1) phosphorylation". *The Journal of Experimental Medicine* **193** (2): 263–9. doi:10.1084/jem.193.2.263. PMC 2193341. PMID 11208867.

[18] Aguirre V, Uchida T, Yenush L, Davis R, White MF (Mar 2000). "The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307)". *The Journal of Biological Chemistry* **275** (12): 9047–54. doi:10.1074/jbc.275.12.9047. PMID 10722755.

[19] Hadari YR, Tzahar E, Nadiv O, Rothenberg P, Roberts CT, LeRoith D, Yarden Y, Zick Y (Sep 1992). "Insulin and insulinomimetic agents induce activation of phosphatidylinositol 3'-kinase upon its association with pp185 (IRS-1) in intact rat livers". *The Journal of Biological Chemistry* **267** (25): 17483–6. PMID 1381348.

[20] Gual P, Gonzalez T, Grémeaux T, Barres R, Le Marchand-Brustel Y, Tanti JF (Jul 2003). "Hyperosmotic stress inhibits insulin receptor substrate-1 function by distinct mechanisms in 3T3-L1 adipocytes". *The Journal of Biological Chemistry* **278** (29): 26550–7. doi:10.1074/jbc.M212273200. PMID 12730242.

[21] Hamer I, Foti M, Emkey R, Cordier-Bussat M, Philippe J, De Meyts P, Maeder C, Kahn CR, Carpentier JL (May 2002). "An arginine to cysteine(252) mutation in insulin receptors from a patient with severe insulin resistance inhibits receptor internalisation but preserves signalling events". *Diabetologia* **45** (5): 657–67. doi:10.1007/s00125-002-0798-5. PMID 12107746.

[22] Xia X, Serrero G (Aug 1999). "Multiple forms of p55PIK, a regulatory subunit of phosphoinositide 3-kinase, are generated by alternative initiation of translation". *The Biochemical Journal* **341** (3): 831–7. doi:10.1042/0264-6021:3410831. PMC 1220424. PMID 10417350.

[23] Mothe I, Delahaye L, Filloux C, Pons S, White MF, Van Obberghen E (Dec 1997). "Interaction of wild type and dominant-negative p55PIK regulatory subunit of phosphatidylinositol 3-kinase with insulin-like growth factor-1 signaling proteins". *Molecular Endocrinology* **11** (13): 1911–23. doi:10.1210/mend.11.13.0029. PMID 9415396.

[24] Lebrun P, Mothe-Satney I, Delahaye L, Van Obberghen E, Baron V (Nov 1998). "Insulin receptor substrate-1 as a signaling molecule for focal adhesion kinase pp125(FAK) and pp60(src)". *The Journal of Biological Chemistry* **273** (48): 32244–53. doi:10.1074/jbc.273.48.32244. PMID 9822703.

[25] Kuhné MR, Pawson T, Lienhard GE, Feng GS (Jun 1993). "The insulin receptor substrate 1 associates with the SH2-containing phosphotyrosine phosphatase Syp". *The Journal of Biological Chemistry* **268** (16): 11479–81. PMID 8505282.

[26] Myers MG, Mendez R, Shi P, Pierce JH, Rhoads R, White MF (Oct 1998). "The COOH-terminal tyrosine phosphorylation sites on IRS-1 bind SHP-2 and negatively regulate insulin signaling". *The Journal of Biological Chemistry* **273** (41): 26908–14. doi:10.1074/jbc.273.41.26908. PMID 9756938.

[27] Goldstein BJ, Bittner-Kowalczyk A, White MF, Harbeck M (Feb 2000). "Tyrosine dephosphorylation and deactivation of insulin receptor substrate-1 by protein-tyrosine phosphatase 1B. Possible facilitation by the formation of a ternary complex with the Grb2 adaptor protein". *The Journal of Biological Chemistry* **275** (6): 4283–9. doi:10.1074/jbc.275.6.4283. PMID 10660596.

[28] Ravichandran LV, Chen H, Li Y, Quon MJ (Oct 2001). "Phosphorylation of PTP1B at Ser(50) by Akt impairs its ability to dephosphorylate the insulin receptor". *Molecular Endocrinology* **15** (10): 1768–80. doi:10.1210/mend.15.10.0711. PMID 11579209.

[29] Craparo A, Freund R, Gustafson TA (Apr 1997). "14-3-3 (epsilon) interacts with the insulin-like growth factor I receptor and insulin receptor substrate I in a phosphoserine-dependent manner". *The Journal of Biological Chemistry* **272** (17): 11663–9. doi:10.1074/jbc.272.17.11663. PMID 9111084.

5 Further reading

- Jiang H, Harris MB, Rothman P (Jun 2000). "IL-4/IL-13 signaling beyond JAK/STAT". *The Journal of Allergy and Clinical Immunology* **105** (6 Pt 1): 1063–70. doi:10.1067/mai.2000.107604. PMID 10856136.
- Bezerra RM, Chadid TT, Altemani CM, Sales TS, Menezes R, Soares MC, Saad ST, Saad MJ (Feb 2004). "Lack of Arg972 polymorphism in the IRS1 gene in Parakanã Brazilian Indians". *Human Biology* **76** (1): 147–51. doi:10.1353/hub.2004.0015. PMID 15222685.
- Gibson SL, Ma Z, Shaw LM (Mar 2007). "Divergent roles for IRS-1 and IRS-2 in breast cancer metastasis". *Cell Cycle* **6** (6): 631–7. doi:10.4161/cc.6.6.3987. PMID 17361103.
- Dearth RK, Cui X, Kim HJ, Hadsell DL, Lee AV (Mar 2007). "Oncogenic transformation by the signaling adaptor proteins insulin receptor substrate (IRS)−1 and IRS-2". *Cell Cycle* **6** (6): 705–13. doi:10.4161/cc.6.6.4035. PMID 17374994.

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