**SnapShot: Insulin Signaling Pathways**

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**Insulin signaling through IRSs/PI3Ks/Akts**

**Negative regulatory mechanisms of insulin signaling**
Insulin Signaling through IRSs/PI3Ks/AKTs
Insulin binding to its receptor (IR) initiates a complex spectrum of biological effects in mammalian cells. Insulin binding activates the IR β subunit tyrosine kinase that phosphorylates IR substrate proteins (IRS proteins). The two major substrates, IRS-1 and IRS-2, are linked to the activation of the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, which is responsible for most of the metabolic actions of insulin, and to the Ras-mitogen-activated protein kinase (MAPK) pathway, which cooperates with the PI3K pathway to control cell proliferation. IR can phosphorylate at least six known substrate proteins that are capable of interacting with five major forms of the PI3K regulatory subunit, which associate with three forms of the PI3K catalytic subunit. The subsequent generation of phosphatidylinositol-3,4,5-triphosphate (PIP3) leads to the activation of the three known isoforms of Akt via the PDK1 kinase. These combinatorial possibilities allow for the incredible diversification and fine-tuning of insulin signaling in normal physiology and disease states.

Metabolic Effects
Insulin signaling to Akt modulates a range of metabolic processes. In myocytes and adipocytes, phosphorylation of the Rab-GTPase-activating proteins AS160 (TBC1D4) and TBC1D1 by multiple kinases, including Akt, promotes glucose uptake. In hepatocytes, insulin-induced repression of genes involved in gluconeogenesis depends, at least in part, on Akt-mediated phosphorylation and inactivation of the forkhead transcription factor FoxO1. Moreover, insulin increases lipogenesis via kinase-dependent pathways involving PI3K, PDK1, PKCζ/C, and SREBP1c. It also increases glycogen synthesis via the GSK3β/glycogen synthase pathway and inhibits lipolysis via the Akt/PDE3B pathway.

Impact on Cell Proliferation and Death
In addition to metabolic effects, insulin has been reported to stimulate cell proliferation and to inhibit apoptosis. Tuberous sclerosis complex 1/2 is phosphorylated by several kinases, including Akt. Phosphorylation suppresses its GTPase-activating protein activity, leading to activation of the mTORC1 activator Rheb, a ras-like small GTPase, which ultimately results in increased cell proliferation through phosphorylation of S6K1 (p70 S6 kinase 1) and stimulation of translation. Insulin signaling also supports proliferation through activation of the Son-of-Sevenless (SOS)-initiated MAP kinase cascade. Insulin inhibits apoptosis via the Akt/BAD axis. Furthermore, insulin signaling in worms and flies has been shown to be involved in the negative regulation of life span via inhibition of FoxO1.

Interestingly, AMP kinase activation by adiponectin receptor signaling cooperates with the insulin signaling to increase glucose uptake via AS160 and/or TBC1D1, whereas this activation slows cell proliferation via inhibition of mTORC1.

Regulatory Control Mechanisms
Insulin signaling and the downstream pathways are subject to multilayered regulatory controls. These mechanisms include feedback loops and pathway responses to diverse stimuli.

Feedback Loops
Control of IR Activity. A nonreceptor-type phosphotyrosine phosphatase, PTP1B, dephosphorylates IR, limiting its activity. However, IR signaling produces H2O2 that inhibits PTP1B, leading to prolonged insulin signaling. An SH2-containing adaptor protein, Grb10, binds and inhibits IR kinase activity. Recently, mTORC1 has been shown to phosphor- ylate and enhance the inhibitory effect of Grb10 on IR.

At the IRS Level. Several serine/threonine kinases are known to phosphorylate and inhibit the recognition of IRS proteins by IR. S6K1, PKCζ, and SREBP1c. It also increases glycogen synthesis via the GSK3β/glycogen synthase pathway and inhibits lipolysis via the Akt/PDE3B pathway.

Induced Regulatory Mechanisms
Control of IR Activity. Proinflammatory cytokines acting through their receptors activate SOCS-3 (suppressor of cytokine signaling-3), which binds to IR and inhibits its ability to recognize IRS and initiate signaling. At the IRS Level. JNK1 activated by various stimuli, such as cytokines, free fatty acids, ER stress, oxidative stress, and insulin, phosphorylates serine residues in the PTB domain of IRS-1, leading to a reduction of tyrosine phosphorylation. PKCζ activated by intracellular lipid accumulation phosphorylates the same residues of IRS-1. Beyond its interaction with the receptor, SOCS-3 also binds to IRS proteins and functions as a ubiquitin ligase, inducing their degradation and reducing their signaling.

REFERENCES