C9. Insulin Signaling - PI3K and Akt (Protein Kinase B)

Type 2 diabetes, in which people become resistant to insulin which leads to high blood sugar and the cascade of health consequences that follow, is pandemic in the world. Hence a brief look at two of the kinases downstream of the insulin receptor tyrosine kinase is warranted. When insulin binds to the receptor tyrosine kinase (RTK), it phosphorylates itself, which then leads to the binding of other proteins to the activated receptor and their phosphorylation. One of these proteins leads to changes in gene transcription. The other, Insulin Receptor Substrate 1, IRS1, a "scaffolding protein" leads to the movement of the GLUT4 protein (Glucose transport protein) to the cell surface. These activities are shown schematically in the figure below.

Figure: Initial Signaling on Binding of Insulin to the Insulin Receptor
After phosphorylation by the activated insulin receptor protein tyrosine kinase, IRS-1 binds phosphatidylinositol 3-kinase (PI3K) that causes phosphorylation of the 3′OH on phosphatidylinositol (PI) in the inner leaflet of the membrane to form PI(3)P. PI3K is a member of a family of kinases that phosphorylates PI. The metabolic pathway centered on PI3K is one of the most mutated in human cancers. PI(3)P in turn recruits to the membrane other inactive kinases, phosphoinositide-dependent kinase 1, PDK1 and Akt, also known as PKB.

Figure: Phosphorylated Phosphatidylinositol derivatives

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\text{X} = \begin{cases} 
\text{PIP, PIP2, PIP3, or PIP4} & \text{PI} \\
\text{PIP2(3,4) or PI(3,4)P} & \text{X = 1′-myo-inositol-3,4-diphosphate} \\
\text{PIP3(3,4,5) or PI(3,4,5)P} & \text{x = 1′-myo-inositol-3,4,5-triphosphate} 
\end{cases}
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On binding of PI(3)P, PDK1 becomes an active kinase, which phosphorylates and activates Akt. The family of three Akt kinases are major Ser/Thr protein kinase that phosphorylates proteins involved in a host of cell activities, including regulation of glucose transport, cell proliferation and death. In the insulin signaling pathway, active (phosphorylated) Akt leads to movement of the GLUT4 protein from intracellular endosomal vesicles to the cell surface, which offers a quicker way to import glucose into the cell that if Akt activated GLUT 4 gene expression.

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