RESEARCH NOTES: Molecular Basis of Obesity-induced Insulin Resistance

Insulin molecules bind to special receptor proteins on the cell surface to promote the uptake of energy-rich glucose by body cells. In type-I diabetes the insulin-producing cells of the pancreas are destroyed. In non-insulin dependent diabetes mellitus (NIDDM), insulin is produced but has difficulty in getting its chemical message into the cell. Such insulin resistance is particularly common in overweight patients; indeed, NIDDM treatment often involves stringent dieting. Tumor necrosis factor (TNF) is known to be involved in the circuitous route by which macroscopic obesity causes molecular trouble for microscopic insulin receptors -- but how?

Drs. A. Karasik and Hannah Kanety and their colleagues have found that TNF can interfere with the ability of insulin to trigger the addition of phosphate groups (phosphorylation) to the tyrosine groups of insulin receptor substrate-1 (IRS-1) protein, the major substrate of the insulin receptor. IRS-1 protein recruits and activates several key enzymes once phosphorylated in response to insulin. TNF interferes with this process by beating insulin to the punch, and phosphorylating the serine groups of IRS-1 first.

Looking at molecules further down in the TNF molecule's usual signaling cascade, the investigators found that sphingomyelinase (SMase) also inhibited insulin-stimulated IRS-1 tyrosine phosphorylation by phosphorylating IRS-1 serine first. Interestingly, SM-ase did not affect either the phosphorylation of the insulin receptor itself, nor insulin's binding to it. Ceramide, a breakdown product released when SMase attacks sphingomyelin (a membrane component), also mimics the action of TNF and SMase on IRS-1. By affecting the ability of IRS-1 and IRS-2, a related protein, to phosphorylate properlyin the presence of insulin, all three insulin competitors interfere with the substrates' ability to act as "docking proteins" which help the insulin receptor activate PI-3 kinase and other effector molecules

To phosphorylate normally, the IRS-1 and IRS-2 proteins must first bind a specific insulin receptor segment (JM peptide, amino acids 943-984) located just inside the cell membrane. When extracts from TNF-treated or Smase-treated cells were incubated with JM-peptide, the binding of both IRS-1 and IRS-2 to the JM-peptide binding region was inhibited, compared to controls. Pre-incubation with high levels of insulin, to mimic hyperinsulinemia, had the same inhibitory effect as TNF; and the inhibition could be reversed by adding alkaline phosphatase to chop off the serine phosphate groups. Both TNF and SMase also markedly reduced the ability of IRS-1 and IRS-2 to bind Grb-2, an adapter molecule, which promotes the activation of ras-protein and mitogen-activated protein kinase. Thus blocking the proper tyrosine (not serine) phosphorylation of IRS-1 and IRS-2 by insulin has far-reaching consequences.

This information may eventually lead to new pharmaceutical interventions capable of restoring normal IRS phosphorylation patterns.

In summary, in normal individuals, insulin leads to IRS tyrosine phosphorylation (pY circles in figure) and normal receptor signaling and negative feedback mechanisms. In abnormal states, such as obesity-induced diabetes, IRS serine phosphorylation (pS boxes in figure) can lead to insulin resistance by reducing IRS-binding to the insulin receptor and to Grb-2, which trigger the two major insulin signaling pathways. This information may eventually lead to new pharmaceutical interventions capable of restoring normal IRS phosphorylation patterns.