OBESITY AND THE ADIPOCYTE

Studies of the mechanism of inhibition of insulin signaling by tumor necrosis factor-α

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Insulin resistance is defined as a smaller than normal response to a given dose of insulin. It is also a ubiquitous correlate of obesity and a central component of non-insulin dependent diabetes mellitus. Insulin resistance causes a wide range of pathological disorders such as dyslipidemia, arteriosclerosis, and cardiovascular disorders. Several lines of evidence indicate that tumor necrosis factor (TNF)-α plays a central role in the insulin resistance observed in obesity. Indeed, it has been observed in animals (Hotamisligil et al. 1993, Hofmann et al. 1994, Hamann et al. 1995), and more recently in humans (Hotamisligil et al. 1995, Kern et al. 1995), that obesity is linked to an overexpression of TNF-α in adipocytes. TNF-α plays a causal role in the insulin-resistant state of experimental animals since neutralization of TNF-α in obese rats increases their insulin sensitivity (Hotamisligil et al. 1993), probably due to the concomitant increase in the tyrosine kinase activity of the insulin receptor (IR) in adipose tissue and muscle (Hotamisligil et al. 1994a). In cell culture, TNF-α interferes with insulin signaling by inhibiting IR tyrosine kinase activity, and tyrosine phosphorylation of one of its substrates, IRS-1. This effect is observed in various cell lines such as adipocytes, fibroblasts, hepatocytes and myeloid cells (Feinstein et al. 1993, Hotamisligil et al. 1994b, Peraldi et al. 1996). At the molecular level, TNF-α induces serine phosphorylation of IRS-1 (Kaney et al. 1995, Hotamisligil et al. 1996), and this modified form of IRS-1 can function as an inhibitor of the IR tyrosine kinase activity in vitro and in intact cells (Hotamisligil et al. 1996). This effect is dependent upon the phosphorylation of IRS-1 and is reversible by dephosphorylation of IRS-1 by alkaline phosphatase. Two pieces of evidence indicate that this mechanism is the one by which TNF-α induces insulin resistance in animals. First, as compared with IRS-1 from lean animals, IRS-1 obtained from adipocytes and muscles of obese rats was also found to inhibit insulin receptor autophosphorylation. Second, in intact cells, the presence of IRS-1 seems to be crucial for TNF-α mediated insulin receptor inhibition. Indeed, 32D cells which lack endogenous IRS-1 are resistant to the effect of TNF-α on insulin receptor phosphorylation. When IRS-1 is expressed ectopically in these cells, insulin-mediated insulin receptor phosphorylation becomes very sensitive to TNF-α.

TNF-α binds with high affinity to two receptors which, besides their ligand binding domain, exhibit no homology. These receptors, p55TNFR and p75TNFR, are glycoproteins with a single transmembrane domain. Both proteins are devoid of any enzymatic activity, but associate with several different intracellular proteins (Vandenabeele et al. 1995). Stimulation of p55TNFR alone is sufficient to inhibit IR and IRS-1 tyrosine phosphorylation with the same potency of stimulation of both TNF receptors. However, there is some reason to believe that p75TNFR could play some role in vivo. First, stimulation of p75TNFR alone induces some inhibition of insulin signaling (although this effect is much smaller than the effect observed after stimulation of p55TNFR). Secondly, p75TNFR binds TNF-α with a higher affinity and a higher dissociation rate than p55TNFR, so that at low TNF-α concentration p75TNFR can ‘concentrate’ locally the ligand and make it available for p55TNFR according to the ‘ligand passing model’. An inhibition of IR and IRS-1 tyrosine phosphorylation is also observed after treatment of the cells with sphingomyelinase and synthetic analogs of ceramide (Peraldi et al. 1996), mediators that have been linked to p55TNFR. This suggests that activation of sphingomyelinase and production of ceramides is likely to be a major pathway used by p55TNFR to inhibit insulin signaling. Ceramides directly activate various enzymes such as PKC-ζ, a membrane-associated kinase which phosphorylates and activates Raf-1, and a ceramide-activated protein phosphatase which is a subtype of heterotrimeric phosphatase 2A. This leads to the activation of a cascade of phosphorylation/dephosphorylation events. It is likely that stimulation of these enzymes leads to modification of IRS-1 and subsequent inhibition of the insulin receptor. Several questions remained to be asked: (i) what is the physiological stimulator of TNF-α production by adipocyte during obesity; (ii) what is the mode of action of TNF-α (autocrine, paracrine, endocrine); (iii) which kinase phosphorylates IRS-1 in response to TNF-α; and
(iv) by which mechanism does IRS-1 inhibit the tyrosine kinase activity of the insulin receptor after TNF-α treatment of the cells? A better understanding of the connection(s) between the TNF-α and the insulin signaling pathways could be important to find a cure for the state of insulin resistance observed during obesity.

References


