Our studies focus on two subjects. One involves insulin signal transduction and the molecular basis of insulin resistance. The second relates to the modulation of cell adhesion and cellular growth by mammalian lectins.

A. Insulin Signal transduction and insulin Resistance

Failure of target cells to respond to insulin, a state known as insulin-resistance, is a major attribute to the pathological manifestations associated with diabetes— an ever-increasing epidemic of the 21st century. In recent studies we found that agents that induce insulin resistance exploit phosphorylation-based negative feedback control mechanisms, otherwise utilized by insulin itself, to uncouple the insulin receptor (IR) from its downstream effectors, the IRS proteins, and thereby terminate insulin signal transduction. Ser/Thr phosphorylation of the IRS proteins (IRS-1 and IRS-2) impairs their interactions with the insulin receptor; abolishes their ability to undergo Tyr phosphorylation thus inhibiting further propagation of insulin signaling. Furthermore, Ser/Thr phosphorylation induces degradation of the IRS proteins. The objective of our present studies is to unravel the molecular basis for this uncoupling. Currently, we focus on three main questions: i. What is the nature of the Ser/Thr kinases that phosphorylate and uncouple IRS proteins from IR; ii. Which Ser/Thr residues are subjected to phosphorylation. iii. What is the fate of the Ser-phosphorylated IRS proteins. We found that PKB (Akt) is a positive regulator of IRS functions. By contrast, phosphorylation of IRS proteins by insulin-stimulated PKCz and Ikk-beta, dissociates the IR-IRS complexes, inhibits their ability to undergo insulin-stimulated Tyr phosphorylation and terminates insulin signaling. We could further demonstrate that these kinases are not only part of a physiological negative feed back control mechanism, triggered by insulin itself, but they are also activated by inducers insulin resistance (Fig. 1). We have recently identified some of the 'inhibitory' Ser sites subjected to phosphorylation and IRS proteins mutated at these sites were generated. These IRS mutants were resistant to the inhibitory effects of prolonged insulin treatment or to the action of inducers of insulin resistance. The mutated IRS proteins, not only better couple to the insulin receptor, but they are also resistant to proteosomal degradation, induced by prolonged insulin treatment. Furthermore, we have recently identified a novel domain of IRS-1, named DIDI,
which directs this insulin-stimulated proteosomal degradation of IRS-1. Deletion of DIDI generates an IRS-1 which is ubiquitinated, still it is resistant to insulin-induced degradation, implicating DIDI as a site regulating post-ubiquitination events in the process of IRS-1 degradation. Collectively, these findings direct us towards potential novel targets aimed at prolongation and potentiation of insulin signalling in the face of conditions that promote insulin resistance and diabetes.

B. Galectin-8 modulates Cell Adhesion and Cell Growth

A different aspect of our work involves studies of galectins, mammalian lectins implicated as mediators of cell adhesion and growth. We focus on galectin-8, cloned by us, whose expression is markedly enhanced in certain tumor cells including prostate cancer. Galectin-8 is a secreted, integrin-binding protein that modulates integrin interactions with the extracellular matrix. Soluble galectin-8 triggers the activation of JNK and PKB/Akt which promote the accumulation of the cyclin-dependent kinase inhibitor, p21, leading to the inhibition of cell growth. In contrast, cell adhesion to immobilized galectin-8 triggers a unique integrin-mediated signaling cascade including Tyr phosphorylation of FAK, Paxillin and P130Cas, as well as activation of a Rho-family GTPases, MAPK and PI3K cascades. This results in massive remodeling of the cellular cytoskeleton, which is characterized by the formation of extensive lamellipodia and actin containing microspikes (Fig. 2). Of no less importance, ligation of integrins by galectin-8 triggers transcription of a unique set of genes, some of which are directly associated with bone remodeling and prostate cancer progression. Hence, modulation of gene expression by galectin-8 may represent a novel attribute associated with cancer development and bone metastasis. Collectively, these findings suggest that galectin-8 can act in different modes, depending on its cellular context and the extracellular environment. Ongoing studies in the lab attempt to elucidate the signalling pathways utilized by galectin-8 to promote its adhesive functions; resolve the mode of secretion of this protein, and generate mice that overexpress galectin-8, or mice that are galectin-8-null. These studies might help clarify the mode of action of galectin-8 and its cellular functions.

Selected publications


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