246e A Comprehensive Insulin Signaling Model for Predicting Phenotypes Using Expression Data
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The insulin signal transduction pathway is an active area of biomedical research. In this pathway, the peptide insulin binds to the insulin receptor, and initiates a complex signal transduction cascade that ultimately results in the transport of the glucose transporter GLUT4 to the plasma membrane. There is currently immense interest in developing a comprehensive mathematical model for this pathway that incorporates newly-uncovered information including feedback mechanisms in the pathway (Sogard P, et al., *Acta Physiol. Scand.*183: 125-126, 2005.).

In this presentation, we will report a comprehensive mathematical model of the insulin signaling pathway. This model will incorporate downstream signaling events between the protein kinases (PKC, Akt) and GLUT4 translocation, based on recent findings in this area. The model will also include recently elucidated feedback mechanisms in this pathway. Both these features enable more accurate prediction of metabolic events by the model, and have not been included in previous models of insulin signaling. In addition, we will report an analysis of the feedback mechanisms in this pathway, from a system dynamics perspective. This is expected to provide insights on regulation within this pathway.

Furthermore, we will report the use of this model to predict insulin sensitivities and phenotypes from experimental gene expression data including microarray analysis of glycerol kinase-knockout (Gyk k/o) mice. Preliminary analysis using the model predicted that certain genes with altered expression in the Gyk k/o mice confer decreased insulin sensitivity. The analysis with the extended model will explain, at least partly, why patients with glycerol kinase deficiency (an inherited human disorder) develop insulin resistance.

The mathematical model reported here will thus provide a novel use of a metabolic engineering tool (pathway analysis) to translate gene expression data into insulin sensitivity, an important biomedical indicator of phenotype.

Keywords: Insulin signaling, GLUT4, mathematical model, microarray, glycerol kinase.