PREPOBEDIA- NOVEL PREP1-DEPENDENT TRANSCRIPTIONAL NETWORKS IN THE CONTROL OF INSULIN SENSITIVITY
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Type 2 diabets and obesity are related conditions representing major components of the metabolic syndrome and one of the most challenging health problems of this century, also because of their growing impact in childhood. Different studies have identified PPAR-gamma coactivator-1 (PGC-1alpha) as a relevant type 2 diabetes susceptibility gene playing an important role in human obesity as well. Subsequent investigations led to the discovery that p160MBP (MybBindingProtein) serves as a PGC-1alpha inhibitor. More recently, we showed that p160MBP is controlled by the Prep1 gene. Prep1 hypomorphic mice feature increase sensitivity to insulin due to raised PGC-1 alpha and decreased p160MBP levels. These mice also exhibit decreased fat body mass. Indeed, we also identified Prep1 in genetic screenings in C. Elegans and mouse ,as a major gene involved in energy homeostasis and obesity. Importantly, we have preliminary data showing Prep1 overexpression in euglycemic first-degree relatives of type 2 diabetics, which are at very high risk of diabetes. This project aims at understanding how Prep1 gene controls insulin sensitivity and determines adipogenesis, obesity and type 2 diabetes in humans. We will: 1: elucidate the molecular basis of Prep1 role in insulin sensitivity and adipogenesis through in vitro and animal model studies; 2: assess the significance of Prep1 function to insulin sensitivity in humans and the role of this gene in type 2 diabetes and its subphenotypes and in other components of the metabolic syndrome; 3: identify Prep1 target genes and establish their potential as targets for novel strategies to treat type 2 diabetes and metabolic syndrome. To achieve these objectives we have built a multidisciplinary network and gathered experts in the Prep1/p160MBP signaling, type 2 diabetes and obesity molecular biology and genetics, human and mouse genetics and high throughput analysis of gene expression and identification of target genes.

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