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Glucose homeostasis and p75^{NTR}

The sweet side of neurotrophin receptor signaling

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The p75 neurotrophin receptor (p75^{NTR}), a member of the tumor necrosis factor receptor (TNFR) superfamily, was originally identified as a receptor for neurotrophins and is expressed in the nervous system and in many non-neuronal tissues such as white adipose tissue (WAT),[1] skeletal muscle[2] and liver.[3] Although the biological functions of p75^{NTR} in the nervous system have been extensively studied,[4] the multiple roles of p75^{NTR} in non-neuronal tissues are currently emerging. Recent studies have shown surprisingly diverse biologic functions for p75^{NTR}, including liver[3] and muscle regeneration,[2] extracellular matrix remodeling[5] and angiogenesis in response to hypoxia.[6] Since p75^{NTR} lacks a catalytic motif, the diversity of its biological functions is attributed to the large number of intracellular adaptor proteins that interact with the intracellular domain of p75^{NTR} (p75^{ICD}) and, in turn, activate multiple signaling pathways.

We reported an unexpected function of p75^{NTR} in the regulation of glucose metabolism, whereby p75^{NTR} controls insulin-stimulated glucose transport and insulin sensitivity.[1] Whole-body glucose metabolism is regulated by a complex communication network involving the adipose tissue, skeletal muscle, liver, pancreas and brain. In normal conditions, these tissues rapidly maintain glucose levels after caloric ingestion or long-term starvation. However, insulin resistance, a key feature of type-2 diabetes, reduces the ability to maintain normal glucose homeostasis, causing decreased glucose disposal and increased hepatic glucose production. We showed that genetic loss of p75^{NTR} lowered glycemic excursions after glucose, increased the hypoglycemic effect of insulin, increased the glucose disposal rate and significantly improved the suppression of hepatic glucose production by insulin.[1] The finding that the *p75$^{NTR-/-}$* mice are more insulin-sensitive when fed normal chow represents an unexpected and unique phenotype, because very few manipulations can enhance insulin sensitivity in normal lean mice, with the exception of caloric restriction.

We next explored the mechanisms by which p75^{NTR} regulates insulin sensitivity in cell autonomous systems. Adipocytes and skeletal muscle myocytes lacking p75^{NTR} had increased glucose uptake resulting from enhanced GLUT4 translocation to the plasma membrane. Overexpression of either full-length p75^{NTR} (p75FL) or p75^{ICD}, which lacks the neurotrophin binding domain, rescued this increase. The addition or inhibition of neurotrophin ligands had no effect on glucose uptake in adipocytes, suggesting that the ability of p75^{NTR} to regulate glucose uptake is neurotrophin-independent. In accordance, previous studies support that p75^{NTR} may exert several neurotrophin-independent functions such as apoptosis,[4] Rho activation[3,7] and regulation of the cAMP/PKA signaling pathway.[5] Our data do not exclude the potential contribution of other co-receptors that interact with p75^{NTR} to regulate glucose uptake. Interestingly, the p75^{NTR} co-receptor sortilin, which regulates cell death functions,[8] is also involved in GLUT4 trafficking.[9] Future studies will examine the potential contribution of the interactions of p75^{NTR} with its co-receptors in the regulation of glucose uptake.

Our study showed that p75^{NTR} regulates glucose uptake via its interaction with the small GTPases Rab5 and Rab31. The Rab5 family of GTPases plays an important role in the regulation of intracellular transport, including GLUT4 transport. Previous reports showed that p75^{NTR} directly binds the GTPases Rho and Ras to regulate neurite formation,[10] and p75^{ICD} is sufficient to induce activation of RhoA[7] and Rac GTPases.[11] Using endogenous co-immunoprecipitation, deletion mapping mutagenesis and peptide array mapping, we identified that Rab5 and Rab31, both members of the Rab5 family of GTPases, interact with p75^{ICD}. Furthermore, we showed that p75^{NTR} differentially modulates their activities, resulting in increased plasma membrane GLUT4 translocation and glucose uptake in *p75$^{NTR-/-}$* adipocytes. In addition, we showed that p75^{NTR} interacts with Gapex-5, a guanine nucleotide exchange factor for Rab5 and Rab31. These findings suggest that p75^{NTR} modulates Rab5 family of GTPases activity. Future studies will examine the specific mechanism by which p75^{NTR} regulates guanine nucleotide exchange factors, such as Gapex-5. Since p75^{NTR} and the Rab5 family of GTPases are expressed in multiple tissues, p75^{NTR}-Rab5 GTPase interactions could represent a general mechanism for the regulation of intracellular trafficking.

In summary, we identified p75^{NTR} as a unique player in glucose metabolism. Our results showing that *p75$^{NTR-/-}$* mice display heightened systemic insulin sensitivity in all three major insulin target tissues, namely fat, muscle and liver, together with the cell-autonomous improvements in insulin action in adipocytes and skeletal muscle cells, suggest a primary role for p75^{NTR} in the regulation

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of glucose homeostasis. It will be of major interest to dissect the tissue-specific role of $p75^{NTR}$ in regulating insulin sensitivity. The regulation of GLUT4 intracellular trafficking by $p75^{NTR}$ through its interaction with Rab5 and Rab31 not only introduces $p75^{NTR}$ as a novel player in the regulation of whole-body glucose homeostasis, but also as a new potential therapeutic target for insulin resistance and type-2 diabetes.

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