Nischarin regulates energy metabolism

Nischarin is a novel protein that is discovered by us. We demonstrated that it functions as a molecular scaffold that holds and interacts with several protein partners in a number of biological processes. Previously we have shown that Nischarin inhibits tumor growth and metastasis. Nischarin contains various domains involved in protein-protein interactions including a Phox domain, a leucine-rich repeat domain, a coiled-coil domain, an integrin-binding domain, a proline-rch domain and the C-terminal domain. In the current study, we have created knockout (mutant) mouse model where we deleted LRR region of gene in the mouse genome, and it resulted in non-functional Nischarin. Using this mouse model, we discovered that Nischarin interacts with and inhibits the activity of AMP activated protein kinase (AMPK). AMPK is a serine/threonine kinase that functions as an intracellular energy sensor and plays an important role in maintaining energy homeostasis. AMPK stimulates ATP-generating pathways including glycolysis and uptake of glucose and fatty acids. AMPK also suppresses ATP consuming pathways such as lipogenesis and protein synthesis. AMPK is a protein which is a downstream effector of LKB1, a protein that we showed interaction with Nischarin. In Nischarin deleted mouse, we found decreased activation of genes that make glucose. Blood glucose levels were lower in the knockout mice, with improved glucose tolerance. Furthermore, our data showed that Nischarin mutation inhibits several genes involved in fat metabolism. The knockout mice displayed increased energy expenditure in spite of their stunted growth and appetite suppression leading to decrease in food intake and weight reduction.

Since Nischarin animals are characteristically small in size, we hypothesized that Nischarin regulates pathways in growth and metabolism. Our data show that suppression of Nischarin leads to greater AMPK activation leading to increased glucose tolerance and suppression of lipogenic gene expression. In summary, suppression of Nischarin may have beneficial effects in preventing several metabolic disorders including type 2 diabetes and obesity. This is because high levels of AMPK activity support glucose oxidation and inhibit lipogenesis. These studies demonstrate the potential of Nischarin as a regulator of metabolic diseases and suggest suppression of Nischarin function may be a valuable approach in the quest to cure various metabolic disorders.

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