Skeletal muscle-specific deletion of MKP-1 reveals a p38 MAPK/JNK/Akt signaling node that regulates obesity-induced insulin resistance

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Abstract

Stress responses promote obesity and insulin resistance, in part, by activating the stress-responsive mitogen-activated protein kinases (MAPKs), p38 MAPK and c-Jun NH_2 kinase (JNK). Stress also induces expression of MAPK phosphatase-1 (MKP-1), which inactivates both JNK and p38 MAPK. However, the equilibrium between JNK/p38 MAPK and MKP-1 signaling in the development of obesity and insulin resistance is unclear. Skeletal muscle is a major tissue involved in energy expenditure and glucose metabolism. In skeletal muscle, MKP-1 is upregulated in high fat-diet fed mice and in skeletal muscle of obese humans. Mice lacking skeletal muscle expression of MKP-1 (MKP1-MKO) showed increased skeletal muscle p38 MAPK and JNK activities and were resistant to the development of diet-induced obesity. MKP1-MKO mice exhibited increased whole-body energy expenditure that was associated with elevated levels of myofiber-associated mitochondrial oxygen consumption. miR-21, a negative regulator of PTEN expression, was upregulated in skeletal muscle of MKP1-MKO mice resulting in increased Akt activity consistent with enhanced insulin sensitivity. Our results demonstrate that skeletal muscle MKP-1 represents a critical signaling node through which inactivation of the p38 MAPK/JNK module promotes obesity and insulin resistance.