

Irisin, its receptor and the links between exercise and health

Exercise has beneficial effects on several organs. These effects are often mediated by myokines, muscle secreted factors for tissue crosstalk. Irisin is a myokine induced by exercise in skeletal muscle. Irisin is a polypeptide of 12kDa that is cleaved from a type I membrane protein called FNDC5. FNDC5 is expressed mainly from skeletal muscle, heart, and brain. FNDC5 mRNA increases in adult human muscles with several forms of endurance exercise. Advanced tandem Mass Spectrometry has demonstrated that human irisin circulates at “hormone-like” levels and increases as a consequence of endurance exercise. Since its discovery in 2012, irisin has been shown to affect bone, fat, and brain. In many cases, irisin’s effects are reminiscent of those derived from physical exercise, including improved cognition and bone remodeling in mice.

Here, we identified the major receptor for irisin as the α V integrin family and its cofactor as cluster of differentiation 81 (CD81) with quantitative proteomics using mass spectrometry. Irisin treatment increased phosphorylation of focal adhesion kinase (FAK), and genetic deletion of CD81 or treatment of integrin α V inhibitors blunted the signaling. Irisin treatment enhanced thermogenic fat cell proliferation and genetic deletion of integrin β 1 or integrin β 5, dimer partners of integrin α V, prevented irisin-induced FAK phosphorylation. Genetic deletion of CD81 blocked irisin-induced thermogenic fat cell proliferation *in vitro* and worsened metabolic phenotypes upon high-fat diet challenge. Overall, this data suggests irisin treatment as a therapeutic approach to metabolic diseases such as obesity and type 2 Diabetes.