OBESITY AND DIABETES

Lipid boosts muscle and shrinks fat

Atrophy — the loss of muscle — is a common problem in ageing and in many diseases. As there is currently no therapy, a compound that is able to reduce atrophy could potentially become a useful drug. Now, Adams and colleagues have identified ursolic acid — a pentacyclic triterpene that is found in apple peel — as such a candidate. Writing in *Cell Metabolism*, they report that enhanced insulin and insulin-like growth factor 1 (IGF1) signalling underlie the effects of ursolic acid, which include reduced adiposity, greater muscle mass and improved levels of glucose and plasma triglycerides.

To allow an unbiased approach in the search for potential compounds, the authors queried the Connectivity Map — a database of the mRNA expression profiles obtained by stimulating human cells with various biologically active small molecules. They compared the Connectivity Map profiles with mRNA profiles obtained from human muscle biopsy samples following two types of atrophy stress — fasting or spinal cord injury. They reasoned that as certain changes in mRNA expression are associated with atrophy, compounds that cause changes in the opposite direction would be of interest.

Ursolic acid was the only compound with an mRNA expression profile that showed a statistically significant negative correlation with the profiles of both the fasting and the spinal cord injury models of atrophy. The authors then showed that ursolic acid increased muscle mass by 7% in fasting mice. Ursolic acid was also effective in mice with denervation-induced hindlimb atrophy. In addition, mice that were fed a normal diet plus ursolic acid had stronger muscles, which shows that ursolic acid both reduces atrophy and enhances hypertrophy.

Next, they looked for clues to the mechanism of action of ursolic acid. In mouse leg muscle, ursolic acid suppressed the transcription of atrogin 1 (also known as *Fbxo32*) and *Murf1* (also known as *Trim63*), two mRNAs that are required for atrophy. These mRNAs are also suppressed by IGF1, which is a powerful activator of AKT signalling that reduces atrophy and promotes hypertrophy. Indeed, *Igf1* mRNA was elevated in these leg muscles but not in adipose tissue. Circulating levels of IGF1 were unchanged.

Knowing that ursolic acid enhances insulin-mediated AKT activation in non-muscle cells, the authors wondered whether its mechanism of action in muscle cells might also involve AKT. In mice, they found that ursolic acid increased AKT phosphorylation. Further experiments showed that mice that were fed a ursolic acid supplement were leaner with reduced levels of plasma triglycerides and cholesterol.

To allow precise measurements, the researchers used an *in vitro* model — C2C12 skeletal muscle myotubes. This model showed that only in the presence of IGF1 or insulin could ursolic acid increase AKT phosphorylation. In addition, ursolic acid enhanced the phosphorylation of key downstream targets of IGF1 signalling — ribosomal S6 kinase and extracellular signal-regulated kinase.

These results show that ursolic acid increases the activity of IGF1 and insulin receptors. The authors say that it may achieve this by inhibiting an enzyme that dephosphorylates these receptors. Further studies will also be needed to determine whether AKT signalling is the only pathway involved, and whether other ursolic acid receptors exist.

Samia Burridge

ORIGINAL RESEARCH PAPER Kunkel, S. D. *et al.* mRNA expression signatures of human skeletal muscle atrophy identify a natural compound that increases muscle mass. *Cell Metab.* **13**, 627–638 (2011)