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Irisin, the novel myokine responsible for benefits of physical exercise on bone

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It has been recently reported that, after physical exercise activity, the skeletal muscle releases Irisin, the newly identified myokine able of driving transition of white adipocytes into brown, following a phenomenon known as the browning response. This result suggested that skeletal muscle is crucial in the regulation of energy homeostasis, supporting its role as endocrine organ that targets adipose tissue by promoting energy expenditure. In accordance with this new finding, we demonstrated that conditioned media (CM) collected from primary myoblasts of exercised mice were able to induce osteoblast differentiation in a greater extent than those of mice housed in resting conditions and this effect is Irisin-mediated. In view of further proving the involvement of Irisin in bone metabolism, we validate its direct effect on osteoblasts by using r-Irisin. Here we show that phosphorylation of MAP kinase ERK and expression of Atf 4 ($p<0,001$), the key trascription factor of osteoblast differentiation, were significantly increased after Irisin treatment. Furthermore, ALP and pro-Collagen I mRNA resulted up regulated ($p<0,001$), as we already demonstrated by treating osteoblasts with conditioned medium from primary myoblasts of exercised mice. To recapitulate *in vivo* the effect of physical exercise, we injected mice with r-Irisin. Our results show that BV/TV of Irisin-treated mice was higher than vehicle-injected mice. In elderly, the severe decline of skeletal muscle function, known as Sarcopenia, is associated with impaired function of bone (Osteopenia) and these two simultaneous losses of function lead to increased risk of bone fractures. In order to reveal new strategies for treatment of sarcopenia and osteopenia, we also analyzed the effect of physical activity in old mice. Our findings demonstrate that mRNA levels of the most relevant bone proteins resulted up regulated in ex-vivo osteoblast obtained from exercised old mice compared with mice kept in resting conditions. Our data highlight a novel link in muscle-fat-bone axis demonstrating that Irisin targets bone tissue directly. Future perspectives, based on these studies, could satisfy the ongoing research of exercise-mimetic therapies with anabolic action on the skeleton.

Keywords

Irisin, physical activity, osteoblast, osteopenia, sarcopenia.