Branched-chain amino acid mixtures promote mitochondrial biogenesis in mammals: signaling mechanisms and clinical relevance in age-related disorders

A. Valerio[1], M. Ragni[2], L. Tedesco[2], C. Ruocco[2], A. Fossati[2], F. Fenaroli[1], M. Bicelli[1], G. D'Antona[3], M.O. Carruba[2] and E. Nisoli[2]

[1]Dept of Molecular and Translational Medicine, University of Brescia, Italy; [2]Dept of Medical Biotechnology and Translational Medicine, University of Milan, Italy; [3]Dept of Molecular Medicine, University of Pavia, Italy

Nutrients are major regulators of biochemistry and physiology in all living organisms, and fine changes in nutrient composition are linked to genetic and epigenetic control of processes linked to survival and healthspan. Though contentious yet, calorie restriction (CR), which defines the reduced intake of calories as foods without malnutrition, postpones the age-related diseases, including muscle degeneration, and hence extends healthspan and lifespan in many species. The molecular basis of this long known phenomenon are still elusive, albeit evidence seem to converge on the reduction of mitochondria-derived oxidants through the generation of new, more efficient organelles (mitochondrial biogenesis) (Nisoli et al., Science 310: 314-317, 2005). Branched-chain amino acids (BCAAs) are known to display several healthy effects both in animals and humans (Valerio et al., Aging 3: 464-478, 2011). Notably, we reported that a BCAA-enriched mixture (BCAAem), differently from other amino acid mixtures, promoted mitochondrial biogenesis in cardiomycytes and skeletal myocytes differentiated in culture, as well as in heart and skeletal muscles of sedentary and trained, middle-aged (16-18 months) mice supplemented for 3 months in drinking water. This was accompanied by improved locomotor activity and coordination and most important by extension of average lifespan (D'Antona et al., Cell Metab 12: 362-372, 2010). Notably, muscle fibers (size and composition, in addition to their ultramicroscopic features) were rejuvenated in aged, supplemented mice. These results would suggest that BCAAem behaves as a CR-mimetic. Thus, more recently, we investigated the effects of the BCAAem supplementation in mice with statin-induced myopathy. Although they are relatively safe drugs, all statins are associated with a significantly elevated risk of myopathy, which in humans can ranges in severity from asymptomatic increases in creatine kinase to muscle weakness, aches, and fatigue, to the rare fatal rhabdomyolysis. Because their use is expected to continue to grow alongside the increasing elderly population, the number of patients who do not tolerate statins due to myopathy-like symptoms is fated to increase significantly in the next few years. Here we report that the BCAAem prevented the atorvastatin- and rosuvastatin-induced structural and functional deterioration of skeletal muscles in both control wild-type and hypercolesterolemic mice (ApoE receptor knockout mice on a high-fat diet). These results suggest that selective amino acid mixtures may avoid statin-myopathy also in humans.