

The Metabolic Approach to Skeletal Muscle Disorders

This issue of Basic and Applied Myology is entirely devoted to the involvement of Skeletal Muscle in different diseases. Aim was to focus on skeletal muscle not only as a target organ, but as a player in many pathophysiological situations. The novelty of the Issue is the holistic approach to these problems. Several diseases have been considered: mitochondrial myopathies, heart failure, cachexia, exercise and ageing.

The first chapter describes in great details muscle homeostasis and emphasizes the role of Carnitine in this contest. Carnitine and its system of proteins in fact intervene in the mitochondrial long-chain fatty acids beta-oxidation pathway, favouring lipid oxidation in skeletal muscle rather than storage in the adipose tissue or in the muscle itself. Abnormalities at the control and regulatory level can alter muscle homeostasis and result in insuline resistance, and changes in body composition leading to obesity.

The contribution of Vescovo and Dalla Libera deals with the heart failure skeletal muscle myopathy. This is characterized by changes in myofibres and isomyosins type and atrophy secondary to myocytes apoptosis. Prevention of isomyosin shift and apoptosis and improvement in muscle health may have positive reflections on exercise capacity and symptoms. These Authors suggest that it is possible to block pharmacologically the apoptotic cascade and therefore prevent muscle waste and atrophy.

In the chapter of Piepoli and Coats is analyzed the origin of symptoms in heart failure patients. They often complain of breathlessness, reduced exercise capacity and muscle fatigue. These symptoms may cause patients to avoid physical activity, which may adversely affect not only the quality of life but also prognosis. This chapter reviews some of the abnormalities that can occur secondarily in extra-cardiac systems during heart failure and explains how they may contribute to exercise limitation and be harmful during the progression of the syndrome.

Di Mauro and colleagues offer an excellent review of disorders affecting skeletal muscle (in particular, mitochondrial myopathies). They first consider myopathies due to defects in mitochondrial DNA (mtDNA), distinguishing those due to defects of mitochondrial protein synthesis *in toto* from those due to mutations in protein-encoding genes. They then divide disorders due to nuclear gene defects into several groups and discuss mitochondrial myopathies due to genetic defects affecting respiratory chain components, the protein importation machinery, the inner membrane lipid milieu, and intergenomic signaling. They make a very interesting point regarding a wide range of neuromuscular affections that are characterized by fibres atrophy and loss.

Over the past years there has been increasing evidence that apoptotic cell death is one of the major contributors of severe muscle atrophy and focal myofiber damage. Apoptosis of multinucleated muscle fibres, with individual nuclei controlling muscle fibres segments, is different from that seen in mononucleated cells and may lead to atrophy rather than cell death. On the other hand, losses of myonuclei in a multinucleated myofiber population are equivalent to cell losses in mononucleated replicating tissues, such as epithelia or cancer cells. In the absence of effective primary treatments, there is some hope that interventions on apoptosis will represent a promising therapeutic strategy, especially in slowly progressive diseases such as muscular dystrophies and post-denervation disorders. As described by Peter J. Adhihetty and David A. Hood, the mechanisms of apoptosis in muscle could be targets of molecular interventions.

As described by Toumi, Fitzsimons and Best, muscle damage and myopathy-like changes can occur following strenuous and uncustomed exercise. Tews addresses the question of how eccentric contractions effect muscle performance and produces muscle injury. The mechanism(s) accounting for the loss of strength is also addressed by focusing attention on the changes in activation and mechanical properties of the muscle.

Wolfram Steinborn and Stefan D Anker approach the problem of muscle waste and cachexia from the neuro-hormonal point of view. Cardiac cachexia is linked to raised plasma levels of tumor necrosis factor alpha and other inflammatory cytokines and increased concentration of epinephrine, norepinephrine, and cortisol. Plasma renin activity and aldosterone levels are also increased. They suggest that cardiac cachexia

may be the result of a multifactorial neuroendocrine and metabolic disorder and of a complex imbalance of different body systems.

Ageing is another situation in which skeletal muscle is profoundly altered by the occurrence of the so called “sarcopenia”, whose development is discussed by Maggi and Colleagues. Alterations in the signalling pathways, physical inactivity, oxidative stress, chronic inflammation, changes in body composition and maybe genetic predisposition may lead to it. Exercise is the only intervention that can prevent and, to a certain extent, reduce sarcopenia in old individuals. However, the relationship between physical activity and the intrinsic process of sarcopenia remains unclear.

I think that this series of valuable contributions may be appreciated by a broad spectrum of readers with clinical or basic science background and form a basis for an integrated approach to muscle disorders.

Menotti Calvani
Direzione Scientifica
SIGMA-TAU s.p.a.
Via Pontina km 30,400
00040 Pomezia (Roma)