Apoptosis and Skeletal Muscle in Aging

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Abstract

Apoptosis is highly considered as a possible mechanism in the aging process of skeletal muscle. Age-related apoptosis pathways in aging skeletal muscle are several, and apoptotic stimuli considered as initiators could be of various type, such as calcium, TNF-α and oxidative stress. In the last decade, scientific research has focused on some topics in order to establish an appropriate lifestyle improving the homeostasis of muscle tissue in aging. Physical exercise seems to improve cellular antioxidant defense especially when associated with a good quality of nutrition, thanks to some nutrients, such as carotenoids and oleic acid that have antioxidant properties. A combination of physical exercise, caloric restriction and diet seems to be best strategy to attenuate apoptotic pathways that lead to the loss of skeletal muscle in aging, with all consequence on the physical well-being of the elderly.

Keywords

Apoptosis, Aging, Skeletal Muscle, Exercise, Nutrition

1. Introduction

Aging is a condition of life characterized by a decline in physical functions which impairs quality life of old people. Age-related decrease in skeletal muscle quantity is known as sarcopenia. However, it should be also considered the quality of muscle tissue that may be crucial as much as the quantity [1]. Aging determines muscle force decline due to a progressive decrease in anabolism with an increase of catabolism. These physiological events are also accompanied by a reduced muscle regeneration capacity. The unbalanced muscle protein turnover and tissue remodeling are associated with impaired muscle cell recruitment and apoptosis [2]. Apoptosis is a regulated mechanism of cell death, characterized by molecular, biochemical and morphological events, considered as a possible mechanism in the aging process of skeletal muscle [3] [4]. Different apoptotic stimuli, such
as oxidative stress, calcium and TNF-α, may be considered as initiators of the apoptotic signaling in aged skeletal muscle [2]-[7]. There are two pathways of apoptosis determining the synthesis of extracellular or intracellular signals promoting cell death (Figure 1) [8], the breakdown of the cytoskeleton promoting cell shrinkage and the destruction of the nuclear envelope and the fragmentation of the DNA [9]-[11] (Figure 2). The extrinsic pathway is activated by pro-apoptotic receptors (ligands) on the cell surface (Figure 1) [8] [12]. The intrinsic pathway of apoptosis is instead regulated by mitochondrial parameters (Figure 1) [11]. Mitochondrial mediated apoptosis may initiate through the release of pro-apoptotic proteins into the cytosol also due to age-related mitochondrial dysfunctions [13] [14]. However, the mitochondria also contain anti-apoptotic proteins [11]. Mitochondrial pro- and anti-apoptotic proteins belong to the B-cell lymphoma-2 (Bcl-2) family [11] and the balance between them determines apoptosis [15].

2. Aged Skeletal Muscle

Age-related apoptosis in skeletal muscle is a topic widely discussed in the scientific literature. Research data reported that in old age the mitochondrial caspase-independent apoptotic pathway, through the apoptosis inducing factor (AIF) and the endonuclease G (Endo G) may play a more relevant role in skeletal muscle loss than caspase-mediated apoptosis, through cytochrome c, Bax/Bcl2 [4] [16]. There is also, thought little, evidence that levels of cytosolic Ca²⁺ increase with age [6] and that in this condition, the activation of the endoplasmic reticulum-mediated apoptotic pathway is stimulated [4]. Degradation and resynthesis of skeletal muscle proteins are

![Figure 1. Schematic illustration of the intrinsic and extrinsic pathways of apoptosis.](image)

![Figure 2. Schematic illustration of the breakdown of the cytoskeleton promoting cell shrinkage and the destruction of the nuclear envelope and the fragmentation of the DNA.](image)
normally continuous but balanced molecular events, however during aging this balance is disrupted by the increased oxidative stress typical of aging [17]. The effects of age-related oxidative stress in skeletal muscle may determine not only this imbalance between protein synthesis and degradation, but also mitochondrial dysfunction and apoptosis by activating some major signaling pathways, leading to reduction in muscle mass and strength [4] [18]. Data from literature indicate that, in aging, increased apoptosis in skeletal muscle cell involves caspase-2 and c-Jun N-terminal kinase (JNK) mediated intrinsic pathway signaling activated by calcium and oxidative stress [19] [20], even if how JNK mediates ROS-induced apoptosis is not well determined [4]. Aging is also associated with increased DNA fragmentation and cleaved caspase-3 in rat skeletal muscle [3]. Finally, it has been shown that TNF-α is one of the primary signals inducing apoptosis in muscle cell, and that increased synthesis of TNF-α in aged skeletal muscle may act as a signal activating death receptors on the cell surface membrane [4] [5]. In addition, reactive oxygen species (ROS) appear to have a role as second messenger for TNF-α in skeletal muscle, activating the nuclear factor κB (NF-κB) either directly or indirectly [4] [21] [22]. The latter is a major pleiotropic transcription factor modulating immune, inflammation, cell survival, and proliferation responses [4] [23]. Aging also affected TNF-α signaling to NF-κB, and, in addition, proteins such as IKKγ, IκBa, and p65, which are responsible for the TNF-α activation of NF-κB, result increased in the aged soleus muscle [4]. In recent studies, NF-κB concentrations resulted four-fold higher in elderly human muscles compared to those of young people, and this increased concentration was accompanied by anabolic signaling deficits observed in debilitated, aging muscle [4] [24]. However, the exact mechanism by which NF-κB acts in aging muscle is still to clarify [4].

3. Discussion

As reported above, age-related apoptosis pathways in skeletal muscle are numerous and not always clear, however a lot of study have been performed in the last decade, in order to establish if an appropriate life-style can improve the status of muscle tissue (and consequently of the musculoskeletal system) in aging [25]. At this regard, physical activity and nutrition are two topics highly considered. Physical exercise causes an increase in oxidative stress but at the same time it stimulates the adaptive response of the body against oxidative stress [26]. This cytoprotection is associated with several changes in gene expression, upregulation of cellular protective mechanisms and remodelling of the muscle structure, including also mitochondrial biogenesis [27]. There are several kinds of physical exercise, and each of them differently interferes with the various molecular mechanisms active in aging skeletal muscle. Endurance exercise enhances protein synthesis, mitochondrial biogenesis and the release of IL-6 resulting in inhibition of TNF-α production, it also may mediate anti-inflammatory and anti-atrophy effects, including the upregulation of PGC-1α in muscle and downregulation of Toll-like receptors [4] [28]-[31]. Treadmill exercise training and resistance training can attenuate both fiber atrophy and pro-apoptotic signaling in aging skeletal muscle [4] [32] [33]. Moreover, resistance training can increase the activity of mitochondrial enzymes, and decreases skeletal muscle TNF-α in elderly humans [4] [33] [34]. A typical cytoprotective response in stressed skeletal muscle is the increased production of heat shock proteins (HSPs) in order to provide protection against subsequent periods of stress damage and to facilitate a rapid recovery and remodelling if damage occurs [27]. It has been seen that HSPs synthesis is induced in skeletal muscle by exercise [35] [36]. Although in aging skeletal muscle gene expression of antioxidant enzymes decreases and ROSs production increases, physically exercise seems to benefit adaptation of cell antioxidant defense system [25] [37] when supported with a good quality of nutrition or with supplementation of exogenous antioxidants in order to achieve an optimal level of defense [38]. For example, TNF-α stimulation of both inflammatory and apoptotic pathways was attenuated in aging rat skeletal muscle when caloric restriction was applied [5] [39]. A good quality of nutritional status can be achieved not only with caloric restriction but also thanks to some natural nutrients that have antioxidant properties, such as carotenoids and oleic acid. The latter is a typical compound of extra-virgin olive oil, a typical nutrient of the Mediterranean diet. In some recent studies, we showed its antioxidants properties not only in skeletal muscle but also in myocardium and cartilage [40]-[42].

4. Conclusion

In conclusion, we can assert that, probably, the best strategy in order to prevent or attenuate physiological molecular pathways that lead to the loss of skeletal muscle in aging, with all consequence on the physical well-being of the elderly, is a combination of physical exercise, caloric restriction and diet. In accordance with other
authors [4], we think that this combination could improve the structure and function of muscle tissue through multiple mechanisms induced by activation of IGF-1/Akt/mTOR, PGC-1α, and/or other pathways including increased protein metabolism, redox balance, mitochondrial biogenesis and anti-inflammatory ability.

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**Conflict of Interest**

The authors declare that do not have any conflict of interest.

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