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Apoptosis in muscle atrophy: Relevance to sarcopenia

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Abstract

The loss of muscle mass with aging, or sarcopenia, is an important contributor to the functional decline and loss of independence observed with aging. Little is known about the role of apoptosis in sarcopenia. Studies in adult animals have shown that apoptosis is involved in the loss of muscle nuclei during acute disuse atrophy, and caspase-3 dependent pathways play an important role in this process. Elevated apoptosis has also been observed in muscles of aged animals, but this does not depend upon caspase-3 pathways to the same extent as disuse atrophy. Moreover, disuse atrophy induced in aged animals is associated with a higher amount of apoptosis than in young and intracellular mechanisms are different from those in young, depending more on caspase-independent pathways. The functional relevance of the increase in apoptosis with respect to the loss of muscle fibers and muscle cross-sectional area with aging remains to be determined and interventions to decrease apoptosis in muscle need to be evaluated.

Keywords: Apoptosis; Muscle atrophy; Aging; Disuse; Sarcopenia; Myonuclear domain

1. Skeletal muscle atrophy and sarcopenia

Skeletal muscle mass declines with advancing age, such that by 60–70 years of age, skeletal muscle mass in humans has decreased by 25–30%, resulting in a significant decrease of muscle strength. The functional impairment resulting from this age-associated loss of muscle mass, i.e. sarcopenia, has far reaching consequences for the elderly: their ability to successfully participate in physical activities and to perform tasks of daily living is impaired and muscle weakness has been found to be a common feature in elderly who suffer falls (Tinetti et al., 1988). Sarcopenia is due to a loss of muscle fibers, as well as a decrease in total cross-sectional area of the remaining muscle fibers (Brooks and Faulkner, 1994; Lexell, 1993) and even though a decrease in physical activity is partly responsible for the sarcopenia, maintenance of activity levels does not appear to completely protect skeletal muscles from age-associated atrophy (Starling et al., 1999). Mechanisms involved in sarcopenia are actively being investigated and include intrinsic as well as extrinsic factors, such as deficient satellite cell recruitment, contraction-induced injury, loss of neuronal innervation, endocrine changes, and an increase in oxidative stress. An important question is whether processes responsible for the loss of muscle mass due to acute disuse are similar to those underlying sarcopenia and additionally, whether disuse in old muscle is similar to that in young. It is important to note that the loss of muscle with acute disuse is not associated with a decrease in muscle cell number, while fiber number decreases with sarcopenia. This review focuses on the possible role of apoptosis in both acute disuse muscle atrophy and sarcopenia, and identifies areas of research that need to be explored.

With respect to apoptosis, skeletal muscle is a unique tissue, because muscle cells, or myofibers, are one of three cell types, along with osteoclasts and cytotrophoblasts that are multinucleated. This aspect of skeletal muscle has led to the concept of the myonuclear domain, which is defined as the theoretical amount of cytoplasm supported by a single muscle fiber nucleus, or myonucleus (protein/DNA) (Cheek, 1985). Even though muscle size can vary considerably under different conditions, the myonuclear

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domain size remains relatively constant, implying a fairly strict regulation of myonuclear number at least in muscles from young adults. This regulation is governed by two opposing processes: (1) the gain of myonuclei by the fusion of muscle stem cells (satellite cells) into hypertrophying muscle fibers and (2) the loss of nuclei in atrophying muscle fiber (for a detailed discussion of changes in myonuclear domain see (Allen et al., 1999)). Both processes are influenced by aging, but in this review the changes in satellite cell function with aging will not be addressed. It has been shown that myonuclear number decreases in muscles undergoing atrophy in a variety of experimental conditions, such as spinal cord isolation and transection, microgravity, hind limb suspension and chronic denervation (Allen et al., 1995, 1996, 1997a,b; Dupont-Versteegden et al., 1999; Dupont-Versteegden et al., 2000; Gallegly et al., 2004; Rodrigues Ade and Schmalbruch, 1995). It is not clear whether the loss of nuclei is a consequence of, or rather contributes to the loss of muscle protein, and this question needs further investigation. The process by which nuclei are eliminated from multinucleated muscle fibers appears to be similar to apoptosis, since it involves chromatin condensation and DNA fragmentation, which are considered hallmarks of cellular apoptosis (see below). However, apoptosis in a multinucleated myofiber should actually be termed 'apoptotic nuclear death' because destruction of the entire cell does not follow the elimination of the nucleus as in mononucleated cells. This brings up the interesting questions of how nuclei within one continuous cytoplasmic area can respond differently to similar signals and how individual nuclei can be undergoing apoptosis without eliminating other nuclei or cellular contents. There is evidence to support the idea that the fate of nuclei can be different, or in other words that nuclei have some autonomy, even though the nuclei are subjected to the same cytoplasmic environment. First, studies in heterokaryons have indicated that apoptosis can occur in one or more nuclei within the same cytoplasm without induction of apoptosis in the other nuclei (Dipasquale and Youle, 1992; Polunovsky et al., 1996). Polunovsky et al. (1996) studied the induction of apoptosis in heterokaryons formed from vascular endothelial cells in difference states of apoptotic susceptibility. They concluded that strict cytoplasmic control of apoptosis was not occurring, but rather that a combination of the state of nuclear susceptibility to apoptosis and the influence of cytosolic apoptotic regulators determined whether apoptotic nuclear death occurred. Secondly, evidence for 'nuclear autonomy' comes from a study investigating the control of transcriptional activity in skeletal muscles (Newlands et al., 1998). Newlands et al. (1998) showed very elegantly that within an individual muscle fiber, not all nuclei are transcriptionally equivalent, but that gene expression seems to be regulated independently between nuclei. Finally, a recent study indicated that nuclei from satellite cells which had recently fused with myofibers were preferentially targeted for apoptosis during atrophy (Siu et al., 2005). Therefore, nuclei which reside in the myofibers in close proximity to each other are capable of responding to similar cytoplasmic signals in distinct manner. Exactly how this nuclear independency is regulated is currently unknown and requires further investigation. Nevertheless, the fact that apoptotic nuclear death occurs without cellular death raises the question whether the mechanisms by which nuclear death occurs in skeletal muscle are distinct from those involved in apoptosis in mononucleated cells where nuclear as well as cytoplasmic contents are cleared.

Nevertheless, the fact that apoptosis plays an important role in skeletal muscle atrophy can be deduced from the observation that it is increased in skeletal muscle in a number of pathological and under some physiological circumstances. Chronic heart failure, motor neuron disorders, skeletal muscle denervation, spinal cord injury, muscular dystrophy, and skeletal muscle atrophy due to hind limb suspension or immobilization are all associated with an increase in apoptosis in affected skeletal muscles, as measured by terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling (TUNEL) or by DNA fragmentation in gel electrophoresis (Adams et al., 1999; Allen et al., 1997a,b; Borisov and Carlson, 2000; Dupont-Versteegden et al., 1999; Podhorska-Okolow et al., 1998; Smith et al., 2000; Tews et al., 1997a,b). In addition, exercise was shown to increase apoptosis when assayed acutely after a bout of exercise (Podhorska-Okolow et al., 1998), but by contrast, exercise training for a period of 8 weeks decreased apoptosis (Siu et al., 2005). Interestingly, we and others have shown that exercise training attenuated the apoptosis induced by disuse (spinal cord injury or hind limb suspension) (Allen et al., 1997a,b; Dupont-Versteegden et al., 1999). Therefore, apoptosis in skeletal muscle seems to be a highly regulated process that may serve distinct functions under different physiological and pathological conditions and a better understanding of pathways involved in the apoptotic response in muscle is warranted.

A brief review of common pathways involved in apoptosis is described below (for more extensive review see (Primeau et al., 2002)) and the involvement of these pathways in skeletal muscle atrophy and sarcopenia is discussed.

2. Apoptosis

Apoptosis, or programmed cell death, is an important process during development in multicellular organisms ensuring the elimination of superfluous tissues, such as webbing between digits, and is also critical for maintenance of tissue homeostasis in adults. The early stage of apoptosis involves death-inducing signals, such as reactive oxygen and nitrogen species, ligands for the death receptors, among which tumor necrosis factor (TNF)-α, imbalances in