The role of Id2 and apoptosis during skeletal muscle remodeling

COLIN SELMAN AND CHRISTIAAN LEEUWENBURG
University of Florida, Biochemistry of Aging Laboratory, College of Health and Human Performance, Gainesville, Florida 32611

RELATIVELY LITTLE IS KNOWN regarding the relevance of apoptosis to skeletal muscle homeostasis and the possible mechanisms involved, although evidence exists indicating that apoptosis may play a role during muscle aging (11, 17), muscular dystrophy (15), muscle denervation (8), and unloading (3, 4). As such, several investigators have attempted to elucidate the factors involved in skeletal muscle apoptosis by employing various experimental paradigms (3, 5, 6, 12, 18, 20). An interesting approach to this field of research is presented by Alway et al. (6) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. These investigators examined the role of Id2, a regulatory transcription factor, during skeletal muscle hypertrophy and subsequent atrophy, and whether this protein was associated with any alterations in skeletal muscle apoptosis. To achieve this, they induced skeletal muscle hypertrophy, muscle atrophy from a hypertrophied state, and, third, a hypertrophy-atrophy-hypertrophy protocol performed in Japanese quail patagialis muscle. In using this model, the authors appear to have circumvented some of the potential complicating factors associated with certain rodent loading-unloading models, e.g., the effects of hindlimb unweighting or immobilization on both feeding and ambulation.

Alway et al. (6) demonstrated that after unloading of 7, 14, or 21 days duration (after 14 days of preloading), ~22%, 12%, and 10%, respectively, of skeletal muscle nuclei stained poly(ADP-ribose)/polymerase (PARP) positive (indicating apoptosis). This was associated with a significant increase in Id2 mRNA, particularly in the 7- and 14-day groups. The data also suggest that changes occur in a time-dependent manner, with the highest quantity of PARP-positive nuclei occurring early after muscle unloading. The level of positively stained nuclei appears considerable, because apoptotic nuclei in human or animal disease models are thought to generally range somewhere between 0.03 and 2.1% of total nuclei (1). It would be interesting to examine if these nuclei are indeed entirely lost from the muscle population; the exact time course in which an apoptotic nucleus is detectable and how many of these nuclei are required to be lost before myocyte integrity and function are affected. The modulation of myonuclear number to maintain a constant nuclear-to-cytoplasm ratio appears central to muscle remodeling in response to injury, aging, adaptation, and disease (4).

The precise mechanisms involved in apoptosis, particularly skeletal muscle-related apoptosis and the actual involvement in skeletal muscle nuclei loss, are not well understood. Future studies, therefore, could examine which stimuli cause the initial activation of apoptosis in skeletal muscle undergoing remodeling. For example, several stimuli exist including cytosolic Ca²⁺, physiologically produced oxidants (e.g., hydrogen peroxide, nitric oxide, and peroxynitrite), and TNF-α, which can initiate an apoptotic event (9, 14, 16). It is also feasible that skeletal muscle apoptosis after loading and unloading events may originate from mitochondrial dysfunction and the release of pro-apoptotic proteins, such as cytochrome c and apoptosis-inducing factor (10, 11, 13, 19). In addition, elevated cytosolic Ca²⁺ provides a favorable environment for the activation of the endoplasmic reticulum-mediated apoptotic pathway (7), whereas TNF-α may signal the activation of death receptors on the cell surface membrane of skeletal muscle (11, 14). Alway et al. (5, 6) examined several cysteine-dependent, aspartate-specific proteases (caspases), which are endoproteases and integral to caspase-dependent apoptosis. This study demonstrated that several caspases, including the receptor-initiated caspase-8, were activated during the unloading phase, suggesting a possible involvement of receptor-mediated apoptosis. A key piece of evidence presented suggesting a relationship between Id2 and apoptosis was the positive correlation between caspase-8 and Id2 (r = +0.87) during the atrophy phase. Moreover, the greatest loss in muscle mass was observed 7 days after wing unloading, which corresponds with the highest levels of caspase activation.

Address for reprint requests and other correspondence: C. Leeuwenburgh, Univ. of Florida, Biochemistry of Aging Laboratory, 25 FLG, Stadium Road, PO Box 118206, Gainesville, FL 32611 (E-mail: cleeuwen@ufl.edu).

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(caspase-3, -7, -8, -10) and Id2 expression. Therefore, this data strongly suggest that activation of these proteolytic caspases may be responsible for the initiation of muscle protein degradation and eventually result in the loss of muscle nuclei and possibly muscle fibers. However, it still remains unclear if classical apoptosis (cell death) actually occurred in any of these muscle fibers. It is feasible that apoptosis in multinucleated cells (such as myocytes) may initiate a multicomplex process of proteolytic activity, resulting in atrophy rather than wholesale cell death of the myocyte (2).

The study of skeletal muscle apoptosis is highly novel, and the paper by Alway et al. (6) contributes significantly to the understanding of the potential role Id2 and apoptosis play during muscle hypertrophy and atrophy, particularly during the period of significant muscle atrophy (5–7 days) after unloading. One potentially interesting question raised by this paper would be whether a reduction in the Id2 response in this model, perhaps through antisense technology, would confer protection against apoptosis. In addition, the effect of muscle atrophy to levels below control muscle mass rather than from the starting point of muscle hypertrophy on Id2 and apoptosis would also be interesting to explore. Through an extension of ambitious and commendable studies such as that of Alway et al. (6), it may be possible to identify the signal transduction pathways implicated in skeletal muscle apoptosis. The information garnered from this could potentially permit the development of interventions that may attenuate the loss of skeletal muscle myocytes and sarcopenia indicative of advancing age.

REFERENCES