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Abstract

The Role of the Androgen Receptor in Skeletal Muscle and Its Utility as a Target for Restoring Muscle Functions †

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Abstract: Aging is accompanied by a progressive decrease in skeletal muscle mass and function. This process is characterized by the decrease of sex steroid hormone levels due to andropause and menopause. The axis androgens/androgen receptor (AR) sustains muscle size through classic (also called genomic) and non-classic (or non-genomic) actions to elicit various biological responses. Non-genomic androgen effects act through the crosstalk of AR with other partners. Recently, a specific interaction has been shown to occur through AR and filamin A or Src in different types of normal and malignant cells. From these interactions, the activation of several downstream effectors (paxillin, FAK, MAPK, Akt) follows. Such events induce cell proliferation and survival as well as metabolic changes. Irrespective of the sex of the individual, the more important signaling hubs linking the AR non-genomic circuit with cytoskeleton organization have been analyzed by the Western blot of lysate proteins from human skeletal muscle biopsies (obtained from both young and old patients) and C2C12 skeletal muscle cells. The phosphorylation of filamin A and paxillin increases in biopsies derived from old patients (>61 years), as compared with those derived from young patients (<58 years). Furthermore, AR is weakly expressed in samples from old patients, as compared with young patients. Consistent with these findings, C2C12 cells express abundant amounts of AR that increase during the differentiation. This latter finding suggests an involvement of the androgen-triggered rapid activation of several signaling effectors (e.g., MAPK, Akt, Src, FAK) in skeletal muscle disease. Taken together, our findings suggest that the downregulation of the androgen signaling, or of the AR expression, is a key node in the pathogenesis of skeletal muscle related to aging, and is thus related to excessive metabolic functions and loss of skeletal muscle. Given the important knowledge gaps with regards to the mechanism by which androgens regulate skeletal mass functions, more research is needed. Other in vitro or in vivo experiments are necessary in order to inform the utility of targeting the non-genomic AR signaling pathways with new selective androgen receptor modulators and to improve the clinical outcome of age-related frailty and sarcopenia.

Keywords: skeletal muscle; aging; androgen receptor; androgens; cell signaling

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