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Chapter

Introductory Chapter: Muscular Dystrophy and Recent Therapeutic Strategy

Kunihiro Sakuma

1. Introduction

Skeletal muscle tissue accounts for almost half of the human body mass. Human health is markedly affected by any deterioration in the material, metabolic, and contractile properties of skeletal muscle. Skeletal muscle is a highly plastic organ that is modulated by various pathways controlling cell and protein turnover.

Loss of muscle is a serious consequence of many chronic diseases and of aging itself. Muscle loss is also common in muscular dystrophy, in which marked loss of various membranous structural proteins occurs around muscle fibers [1]. Defects in components of the dystrophin-glycoprotein complex (DGC) are known to be an important cause of different muscular dystrophy.

Nowadays, the autophagy-dependent system and ubiquitin-proteasome signaling (UPS) are well known as a major intracellular degradation system, and its appropriate function is crucial to health and muscle homeostasis. Indeed, muscle wasting and weakness such as cachexia, dystrophy, and sarcopenia is characterized by marked decreases in the protein content, muscle fiber size, and muscle strength. Interestingly, a functional defect in autophagy-dependent signaling in sarcopenic mice and humans was recently suggested [2, 3]. In addition, apparent defect of autophagy-dependent signaling is also observed in various muscular dystrophies. Indeed, De Palma et al. [4] have described marked defect of autophagy in dystrophin-deficient mdx mice and Duchenne muscular dystrophy (DMD) patients through the electron microscopic evaluation of muscle tissue and decreased autophagic regulator proteins (i.e., Bnip3, Atg12, and LC3-II). The adaptive changes of UPS are highly controversial in several muscular dystrophies such as DMD, LGMD, and Ullrich congenital muscular dystrophy [5], although UPS seems to not be activated in human sarcopenic muscle [6].

2. Various therapeutic approaches for muscle dystrophy

To attenuate various forms of muscular dystrophy, many researchers have investigated exercise-based, supplemental, pharmacological, and gene therapy approaches. Currently, there is no cure for patients suffering from muscular dystrophies. Although several researchers actively try to determine the effect of pharmacological inhibition of myostatin for DMD patients, it is heavily difficult to obtain positive effects and there are few possibilities for clinical application. Indeed, a randomized clinical trial of anti-myostatin for DMD patients had a trend toward improved muscle mass and performance, but was stopped early due to non-muscle

side effects (i.e., epistaxis and telangiectasias) [7]. Glucocorticoids (GCs) are commonly used and still serve as a gold standard therapy, acting as anti-inflammatory drugs [8]. More recently, weekly, intermittent GCs treatment has been shown to provide a better alternative to a daily regimen without eliciting muscle atrophy [9]. Recently, more attention is paid to induced pluripotent stem cells (iPSCs) technology and their potential application in DMD treatment [10], although almost all studies used DMD model mdx mice. In addition, the strategy using CRISPR/Cas9 technology progressed dramatically for the restoration of functional dystrophin [11]. Young et al. [12] have found that removal of exons 45–55 resulted in the expression of the stable dystrophin protein in both cardiomyocytes and skeletal myotube in vitro. An increasing number of studies report successful and beneficial effects of CRISPR/Cas9 only animal models of muscular dystrophy. Thus, it seems to be necessary for substantial time for genome editing tools to apply the dystrophic patients.

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