Molecular Mechanism and Development of Antisense Therapy for Duchenne Muscular Dystrophy

Akinori Nakamura1,2*

1Intractable Disease Care Center, Shinshu University School of Medicine, Japan
2Department of Medicine (Neurology and Rheumatology); Shinshu University School of Medicine, Japan

EDITORIAL

Muscular dystrophies are a group of inherited and progressive muscle disorders characterized by muscle fiber degeneration and necrosis. Among them, Duchenne muscular dystrophy (DMD), an X-linked disorder, is the most frequent and severe. The patients show disturbances in sitting up or gait at infancy, and die at an age of 30–40 years due to either respiratory or cardiac failure. DMD is caused by a mutation in the DMD gene encoding dystrophin, which is expressed at the sarcolemma of muscle fibers. Dystrophin-deficient muscle presents with various histopathologies such as necrosis, inflammatory cell infiltration, regeneration, or adipofibrosis; therefore, its molecular mechanism is very complex. Furthermore, no permanent therapy is available despite the fact that extensive research on therapeutic strategies has been performed.

I and my colleagues have previously focused on the role of intracellular signaling pathways on the pathogenic mechanism of DMD. In particular, we have determined that mitogen activated protein kinases (MAPKs) could be associated with the dystrophic pathology in the dystrophic cardiac and skeletal muscle of DMD model mice (e.g., mdx) [1-3]. We have also revealed the expression and localization of MAPK downstream molecules, matrix-metalloproteinases-2 (MMP-2) and matrix-metalloproteinases-9 (MMP-9), in the dystrophic skeletal muscle [3,4], and MMP-2 ablation caused a reduction in angiogenesis, which resulted in impaired dystrophic muscle regeneration [5]. To further our understanding of dystrophic pathology, an appropriate animal model for DMD is needed. Compared to murine models, dystrophic dogs show a very similar phenotype and histopathology to that of DMD [6]. Using dystrophic dogs, a selective vacuolar degeneration of Purkinje fibers was found in the early stage of the disease, and activation of μ-calpain (calcium-dependent proteinase) and dislocation of utrophin (dystrophin homologue) with overexpression of Dp71 (truncated dystrophin isoform) could be involved in the pathology [7]. Dystrophic dogs showed a very severe condition with a dramatic increase in serum creatin kinase at the neonatal stage [6]. Very recently, we have reported that the initial pulmonary respiration caused massive diaphragm damage; thereby, leading to high serum creatin kinase levels and respiratory failure. Moreover, in the diaphragm, osteopontin was prominently upregulated prior to the respiration, and immediate-early genes (c-fos, EGR-1) and inflammation/immune response genes (IL-6, IL-8, cyclooxygenase-2, selectin E) were distinctly overexpressed after the respiratory damage [8]. Taken together, these results indicate the identified genes and molecules could be biomarkers of muscle damage and potential targets in pharmaceutical therapies. Thus, many genes and molecules can play a role in certain stages of the disease, and understanding their mechanism of action will help to elucidate the pathology of DMD.

In the development of therapy for DMD, various strategies for gene therapy with viral vectors, stem cell transplantation, or pharmaceutical therapies have been extensively developed. Among them, exon-skipping therapy using antisense oligonucleotides (antisense therapy) has now been applied to DMD. Antisense therapy can change a disrupted open reading frame (out-of-frame) into an in-frame of the DMD gene and help produce a shortened but functional dystrophin at the sarcolemma, subsequently resulting in a milder phenotype. We have previously reported that an antisense therapy corrected the reading frames of the amino acids leading to restoration of dystrophin expression and muscle function in dystrophic dogs [9]. In addition, we have demonstrated a successful systemic rescue of in-frame dystrophin and muscle function by exon 51-skipping in mice harboring a deletion mutation of exon 52 (mdx52) [10], which provide support to ongoing systemic exon 51-skipping clinical trials for DMD [11]. However, exon-skipping treatment is a tailor-made treatment based on each type of gene mutation, and there is uncertainty in the function and stability of each resulting truncated dystrophin. It has been recognized that more than 60% of DMD patients have deletion mutations within exons 45–55 in the gene. Moreover, we and other researchers previously reported that patients having an exon 45–55 deletion showed exceptionally mild or asymptomatic phenotype [12,13].
Taken together, this means that antisense mediated exon 45–55 skipping could be applicable not only to DMD patients but also to severe BMD patients with mutations within exon 45–55, and it has the potential to convert them to a very mild phenotype [11,13,14]. Recently, we have developed an exon 45–55 skipping strategy and subsequently generated systemic dystrophin expression in the dystrophic skeletal muscles of mdx52 without any toxicity [15]. This multi-exon skipping strategy is likely the most promising therapeutic approach in the near future.

Further investigations about the molecular mechanism and development therapy in DMD could have a large impact on not only other muscular dystrophies but also intractable hereditary neuromuscular disorders.

ACKNOWLEDGEMENTS

I would like to thank Dr. Shin’ichi Takeda (National Center of Neurology and Psychiatry) for his supervision.

REFERENCES


