

Human cytomegalovirus IE1 promoter/enhancer drives variable gene expression in all fiber types in transgenic mouse skeletal muscle

ABSTRACT

The CMV IE1 promoter/enhancer is not restricted to the four fiber types, but it can still drive germ-line transgene expression. This is problematic because some fibers express the gene at higher levels due to regional differences in overall expression levels and within-fiber-type variability. The multinucleate syncytial nature of muscle fibers makes it unlikely that variability in this trait is caused by variegating heterochromatinization. Nevertheless, the soleus muscle would be an ideal target for CMV IE1 elements that drive near-uniform experimental gene expression.

INTRODUCTION

The primary explanations for muscular dystrophy triggered by dystrophin deficiency suggest that the absence of this membrane cytoskeletal component compromises sarcolemmal integrity, induces abnormal Ca^{2+} -homeostasis, and/or interferes with accurate clustering of ion channel complexes. Biochemical and cell biological investigations have revealed that muscle dystrophin plays a crucial role as an actin-binding protein, mediating the connection between laminin and the sub-sarcolemmal membrane cytoskeleton. α -, elongin, and ciliary gland cartilage serve as binding sites for several integrator or surface-associated proteins associated with dystrophin. The carboxy-terminus of 43 kDa α -dystroglycan contains a binding site for the second half of the hinge-4 region and the cysteine-rich domain of Dp27, which indirectly links the actin membrane cytoskeleton to the surface membrane through the amino-end of dystrophin molecule. Due to its close association with the peripheral merosin-binding protein α -dystroglycan, this complex offers stable connectivity to the basal lamina's laminin oligosaccharide group (2-chain). Dystrophin deficiency leads to the disintegration of sarcolemmal components and increases the vulnerability of muscle fibers in individuals with Duchenne muscular dystrophy (DMD). Similarly to the pathobiochemical results in DMD, the dystrophic animal model mdx mouse also displays a significant decrease in all dystrophin-associated glycoproteins in bulk skeletal muscle. This could potentially explain why dystrogen-deficient muscle fibres are less stable at the osmotic level and more susceptible to stretch-induced injury. Cytosolic Ca^{2+} depletion may trigger a significant increase in the net protein degradation and could be regarded as paving the way for the molecular pathogenesis of inherited muscular dystrophy. The involvement of other components of the dystrophin-glycoprotein complex in DMD pathology is indicated by the fact that some forms of limb-girdle muscular dystrophy and congenital muscular Dysplasia are caused by primary abnormalities in sarcoglycans and laminin, respectively. While muscle is a more common cause of neuromuscular disease than brain abnormalities, the molecular mechanisms underlying these disorders are much less understood in comparison to human muscle; it is likely that one reason why pathophysiological studies of the dystrophic central nervous system is difficult is due to the greater complexity of dystrophylaxis and utrophin isoforms in the brain. The human DMD gene produces dystrophin protein (Dp) isoforms that are tissue-specific, with seven promoters promoting their expression. Furthermore, dystrophin-related proteins such as brain DRP-2 and utrophin, which encode the autosomal recess forming a full-length 395 kDa isoform (Up395) and two truncated molecular species Up116 and Up71, also known as G- and U-utrophin. The major dystrophin isoform in the

central nervous system is Dp71, which shares a low-abundance form called brain Dpp140 and full-length braindp427. Dp427 was found to be present in cortical neurons, hippocampal neurons and cerebellar Purkinje cells, likely associated with these cell types due to their postsynaptic density, while the two smaller dystrophin brain isoforms were identified as being associated only with microvascular glial cells. Dystroglycans are also found in the brain and a subpopulation that only localizes to the glial-vascular interface. The development of dystrophin expression in perivascular astrocytes coincides with the formation of the blood-brain barrier, according to et al.'s findings. Dystrophin-related proteins are more widespread in the central nervous system, and full-length utrophin may play a role in maintaining regional specialization of the brain. To further investigate the fate of dystroglycans in dystrophin-deficient forebrain using two established genetic animal models, we conducted preliminary research and applied them in tandem. A point mutation in exon 23 of the mdx mouse leads to the loss of Dp427, whereas a mutation at exone 65 of that of an eukaryotic wolff's egg causes the disruption of both dystrophin 4.8 and 14 kb RNAs, leading to further loss (Dp417). Modest modifications in associative learning and deficits in long-term consolidation memory are observed in the dystrophic animal models used in this study, according to neurobehavioral studies. Upon examination of the mutant strains, it is evident that the -dystroglycan is located at the endothelial-glial interface in the forebrain, and not all dystrophic brain cells are reduced to this extent, distinguishing them from dystrophic muscle fibres. An impaired oligomerization of the major brain Dp71 isoform may be responsible for molecular pathogenesis in the dystrophic central nervous system.

CONCLUSION

By describing the building blocks of protein complexes in skeletal muscle and heart, with emphasis on information about genotype-phenotype relationships, we can better understand the pathophysiology of human muscle diseases. Our recommendation is for other groups to test for the C598T DMN mutation in their human patient samples affected by muscular and cardiac diseases. The generation of desmuslin null animal models will also help us comprehend the role of this protein in muscle and cardiovascular disease.