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THE ROLE OF THE DYSTROPHIN–GLYCOPROTEIN COMPLEX IN THE MOLECULAR PATHOGENESIS OF MUSCULAR DYSTROPHIES

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Abstract—The dystrophin–glycoprotein complex is considered to be a major trans-sarcolemmal structure which provides a linkage between the subsarcolemmal actin cytoskeleton and the extracellular matrix component laminin. Recently, deficiency of the dystrophin-associated proteins has been shown to play an important role in the molecular pathogenesis of several forms of muscular dystrophy. These include Duchenne muscular dystrophy (DMD), symptomatic DMD carriers, Becker muscular dystrophy and severe childhood autosomal recessive muscular dystrophy with DMD-like phenotype prevalent in North Africa. In Fukuyama-type congenital muscular dystrophy (FCMD), the finding of abnormal expression of the dystrophin-associated proteins may provide a clue to its molecular pathogenesis. These recent findings indicate that the linkage between the subsarcolemmal cytoskeleton and extracellular matrix via the dystrophin–glycoprotein complex is critical for maintaining the integrity of muscle cell function.

Key words: Dystrophin–glycoprotein complex, dystrophin-associated proteins, dystroglycan, Duchenne/Becker muscular dystrophy, severe childhood autosomal recessive muscular dystrophy, Fukuyama-type congenital muscular dystrophy.

THE STRUCTURAL ORGANIZATION OF THE DYSTROPHIN–GLYCOPROTEIN COMPLEX

In skeletal muscle, dystrophin is associated with a large oligomeric complex of novel sarcolemmal proteins comprised of an extracellular glycoprotein of 156 kDa, three transmembrane glycoproteins of 50 kDa, 43 kDa and 35 kDa, a transmembrane protein of 25 kDa and a cytoskeletal protein of 59 kDa [1–4]. The 156/43 kDa dystrophin-associated glycoproteins are encoded by a single gene and are now called dystroglycan [4]. The 156 kDa dystroglycan binds the extracellular matrix component laminin with high affinity [4]. Dystrophin has been shown to interact with F-actin [5, 6]. Dystrophin constitutes 2% of the total sarcolemmal proteins and 5% of total sarcolemmal cytoskeletal proteins [7, 8]. These findings indicate that the dystrophin–glycoprotein complex is a major trans-sarcolemmal structure which links the subsarcolemmal actin cytoskeleton to the extracellular matrix component laminin.

THE ROLE OF THE DYSTROPHIN–GLYCOPROTEIN COMPLEX IN THE MOLECULAR PATHOGENESIS OF MUSCULAR DYSTROPHIES

There are several forms of muscular dystrophies where deficiency of the components of the dystrophin–glycoprotein complex appears to play an important role in their molecular pathogenesis.

Duchenne muscular dystrophy (DMD)

DMD is caused by the absence of dystrophin which is due to the defects in the dystrophin gene. However, the mechanism by which the absence of dystrophin leads to muscle cell necrosis in this devastating disease has been unclear until recently. The structural organization of the dystrophin–glycoprotein complex suggested that the absence of dystrophin may disrupt the linkage of the dystrophin-associated proteins to the subsarcolemmal actin cytoskeleton in DMD skeletal muscle. This could lead to the dysfunc-

tion of the complex and/or the loss of the dystrophin-associated proteins in the sarcolemma.

Immunohistochemical and immunoblot analyses reveal a great reduction in all the dystrophin-associated proteins in DMD patients of various ages and severity [9]. Based on these results, we have proposed that the disruption of the dystrophin–glycoprotein complex plays a key role in the cascade of events leading to muscle cell necrosis in DMD [9]. The absence of dystrophin causes the disruption of the linkage of the dystrophin-associated proteins to the subsarcolemmal cytoskeleton, leading to a great reduction in all of these proteins. The resulting disruption of the linkage between the subsarcolemmal cytoskeleton and extracellular matrix may lead to sarcolemmal instability and eventually to muscle cell necrosis in DMD [9].

DMD patients lacking the C-terminal domains of dystrophin

Dystrophin lacking the C-terminal domains of dystrophin is expressed along the sarcolemma in some patients with the phenotype of DMD. In these patients, the dystrophin-associated proteins are reduced to the same level as in typical DMD patients [10]. This indicates that the glycoprotein-binding site in the C-terminal domains is missing [11] and this causes the loss of the dystrophin-associated proteins in these patients [10]. These cases suggest that the status of the dystrophin-associated proteins may be more directly correlated with the severity of the phenotype than the status of dystrophin itself.

Symptomatic DMD carriers

In symptomatic DMD carriers, some of the muscle cells are known to be deficient in dystrophin. These muscle cells are also deficient in the dystrophin-associated proteins [12]. Thus, instability of the sarcolemma similar to that in DMD may play an important role in the muscle cell degeneration in symptomatic DMD carriers.

Becker muscular dystrophy (BMD)

In BMD patients with in-frame deletions in the rod domain of dystrophin, there is a mild reduction in the density of the dystrophin–glycoprotein complex in the sarcolemma [13]. In these patients, two important domains of dystrophin, the actin-binding site in the N-terminal domain and the glycoprotein-binding site in the C-terminal domains, are presumed to be preserved, indicating that the linkage between the subsarcolemmal cytoskeleton and extracellular matrix is also preserved. However, dystrophin lacking certain regions of the rod domain may be unstable or may not function normally, and this may lead to the reduction in the density of the dystrophin–glycoprotein complex in the sarcolemma, and eventually muscle cell degeneration.

Severe childhood autosomal recessive muscular dystrophy with DMD-like phenotype (SCARMD)

SCARMD is characterized by the specific deficiency of the 50 kDa dystrophin-associated glycoprotein (50DAG) in the sarcolemma [14]. Other components of the dystrophin–glycoprotein complex are relatively well preserved, except the 35 kDa dystrophin-associated glycoprotein which seems to be reduced secondary to the deficiency of the 50DAG [14]. Recently Syrian cardiomyopathic hamsters have been shown to be deficient in the 50DAG in skeletal and cardiac muscle [15]. Although it remains to be clarified if the same genetic abnormality is responsible for these two conditions, this hamster could be useful as an animal model of SCARMD.

Fukuyama-type congenital muscular dystrophy (FCMD)

FCMD is characterized by the combination of a severe brain anomaly and muscular dystrophy. In FCMD patients, abnormal expression of the dystrophin-associated proteins can be observed: muscle cells are frequently deficient in these proteins, but cells may show abnormally intense staining of the sarcolemma or diffuse cytoplasmic staining for these proteins [16]. However, this abnormality is not as uniform as in the case of 50DAG-deficient SCARMD, and may vary among different FCMD patients [16].

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REFERENCES

1. Campbell K P, Kahl S D. Association of dystrophin and an integral membrane glycoprotein. *Nature* 1989; **338**: 259–262.
2. Ervasti J M, Ohlendieck K, Kahl S D, Gaver M G, Campbell K P. Deficiency of a glycoprotein component of the dystrophin complex in dystrophic muscle. *Nature* 1990; **345**: 315–319.

3. Ervasti J M, Campbell K P. Membrane organization of the dystrophin–glycoprotein complex. *Cell* 1991; **66**: 1121–1131.
4. Ibraghimov-Beskrovnaya O, Ervasti J M, Leveille C J, Slaughter C A, Sernett S W, Campbell K P. Primary structure of dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. *Nature* 1992; **355**: 696–702.
5. Hemmings L, Kuhlmann P A, Critchley D R. Analysis of the actin-binding domain of α-actinin by mutagenesis and demonstration that dystrophin contains a functionally homologous domain. *J Cell Biol* 1992; **116**: 1369–1380.
6. Way M, Pope B, Cross R A, Kendrick-Jones J, Weeds A G. Expression of the N-terminal domain of dystrophin in *E. coli* and demonstration of binding to F-actin. *FEBS Lett* 1992; **301**: 243–245.
7. Ohlendieck K, Ervasti J M, Snook J B, Campbell K P. Dystrophin–glycoprotein complex is highly enriched in isolated skeletal muscle sarcolemma. *J Cell Biol* 1991; **112**: 135–148.
8. Ohlendieck K, Campbell K P. Dystrophin constitutes 5% of membrane cytoskeleton in skeletal muscle. *FEBS Lett* 1991; **283**: 230–234.
9. Ohlendieck K, Matsumura K, Ionasescu V V, *et al.* Duchenne muscular dystrophy: deficiency of dystrophin-associated proteins in the sarcolemma. *Neurology* 1993; **43**: 795–800.
10. Matsumura K, Tomé F M S, Ionasescu V V, *et al.* Deficiency of dystrophin-associated proteins in Duchenne muscular dystrophy patients lacking C-terminal domains of dystrophin. *J Clin Invest* 1993; **92**: 866–871.
11. Suzuki A, Yoshida M, Yamamoto H, Ozawa E. Glycoprotein-binding site of dystrophin is confined to the cysteine-rich domain and the first half of the carboxyl-terminal domain. *FEBS Lett* 1992; **308**: 154–160.
12. Matsumura K, Nonaka I, Arahata K, Campbell K P. Partial deficiency of dystrophin-associated proteins in a young girl with sporadic myopathy and normal karyotype. *Neurology* 1993; **43**: 1267–1268.
13. Matsumura K, Nonaka I, Tomé F M S, *et al.* Mild deficiency of dystrophin-associated proteins in Becker muscular dystrophy patients having in-frame deletions in the rod domain of dystrophin. *Am J Hum Genet* 1993; **53**: 409–416.
14. Matsumura K, Tomé F M S, Collin H, *et al.* Deficiency of the 50 K dystrophin-associated glycoprotein in severe childhood autosomal recessive muscular dystrophy. *Nature* 1992; **359**: 320–322.
15. Roberds S L, Ervasti J M, Anderson R D, *et al.* Disruption of the dystrophin–glycoprotein complex in the cardiomyopathic hamster. *J Biol Chem* 1993; **268**: 11496–11499.
16. Matsumura K, Nonaka I, Campbell K P. Abnormal expression of dystrophin-associated proteins in Fukuyama-type congenital muscular dystrophy. *Lancet* 1993; **341**: 521–522.