

Dystrophin: the long and short of it.

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Editorial

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One important consequence of cloning the gene that is defective in boys with Duchenne muscular dystrophy (DMD) was the identification of its protein product, dystrophin (1). This high molecular weight, cytoskeletal, membrane-associated protein is missing from muscle of boys with DMD and reduced in amount or structurally altered in boys or men with the milder Becker muscular dystrophy (BMD). Its absence is clearly responsible for DMD, but why? What does dystrophin do that is so important?

From its amino acid sequence dystrophin is similar to spectrin and other cytoskeletal proteins: rather like an I-beam with globular domains at each end, joined by a rod-like segment in the middle. At one end (the NH₂-terminal end) dystrophin binds to actin filaments (not actin of the contractile apparatus) inside the cytoplasm (2). At the other end of the molecule dystrophin is bound to a complex of proteins and glycoproteins that copurify with dystrophin from muscle membrane (3). In a series of elegant studies from Campbell and colleagues (4–6) the components of this complex have been identified and characterized from rabbit muscle. Campbell calls them dystrophin-associated proteins (DAPs) and dystrophin-associated glycoproteins (DAGs), and gives them individual names according to their molecular weights: thus, 25DAP, 35DAG, 43DAG, 50DAG, 59DAP, and 156DAG. The 59DAP seems to be on the inside of the cell and binds directly to dystrophin. The 25DAP and the 35, 43, and 50DAGs are transmembrane proteins, four of which have sugar groups on the outer surface of the cell. The 156DAG, also called dystroglycan, seems to be totally outside the cell, is covered with sugar groups, and binds to laminin, a major component of the extracellular matrix (6).

So now we have a picture of an I-beam, one end placed in the wall, the other sticking into the room and attaching to structures in the room. In DMD the beam is gone, usually caused by deletions that alter the reading frame of the message, effectively lopping off the end that binds glycoprotein. Surprisingly, the glycoprotein complex is also absent from DMD muscle membrane, suggesting that dystrophin is necessary to hold the complex in place.

What happens in the milder BMD? In most cases the beam is shorter (the two ends are normal but the rod segment is reduced) due to a non-frame-shifting deletion from the rod-encoding segment of the gene. What happens to the glycoproteins in this case is the subject of a paper from the Campbell group (Matsumura et al.) in this issue of *The Journal* (7). Matsumura et al. have studied rare BMD patients with very large deletions that remove most of the dystrophin rod domain and determined what happens to the glycoproteins in the presence of the very short I-beams. In six patients studied with deletions confined to the rod domain, immunostaining for the DAGs and DAPs showed a slightly reduced intensity with a patchy appearance. In two patients whose deletion extended into the NH₂-terminal domain, the immunostaining was reduced fur-

ther. Both of these boys had a more severe phenotype than the previous six. In general the amount of DAG and DAP staining correlated with the amount of dystrophin staining. The result is not surprising: more dystrophin, more glycoprotein complex in the membrane, and better prognosis.

In essence, any moderation of the phenotype seems to depend on the amount of glycoprotein complex in the membrane, which in turn depends on the amount of dystrophin with intact ends. According to this model one might expect genetic defects in some or all of the DAGs and DAPs to result in a similar form of muscular dystrophy, even in the presence of normal dystrophin. This may be the case. In severe childhood autosomal recessive muscular dystrophy prevalent in north Africa, immunostaining for dystrophin is normal but the 50DAG immunostaining is drastically diminished (8). Whether this is due to a primary defect in the structure or expression of the 50DAG gene has not yet been determined. Interestingly, an autosomal recessive form of cardiomyopathy and skeletal myopathy in the hamster is associated with specific deficiency of the 50DAG protein (9).

We still do not know if dystrophin plays a purely mechanical role in providing strength to the membrane or whether its role is more subtle. The biological role of dystrophin might be, for example, to maintain a particular spatial distribution of the glycoprotein complex. Since the biological function of the complex is essentially unknown, the next leap in our knowledge will come with the cloning and characterization of genes encoding all the DAGs and DAPs. The Campbell group would appear up to the task.

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