con becomes more chemically stable when oxidized, and the interface between silicon and silicon oxide is known to have very few of the undesirable surface states that can quench light emission. Silicon oxides are also compatible with the many processes used in silicon-circuit manufacture, and can probably withstand the subsequent processing steps needed for functional circuits, allowing the successful integration demonstrated by Hirschman *et al.*

One caution is that fields like these can become like the search for the Holy Grail. The search inspires, but it may not be clear exactly what to do, or what the actual benefit is, if the Grail is found. For some applications, such as densely packed optical interconnection to and from silicon electronics, even the very best light-emitting diodes are doubtful candidates because of the fundamental inefficiency of incoherent light emission. In this application, integrating III–V optoelectronic devices (such as high-performance modulators or lasers) with silicon circuitry may be more promising, and may incidentally allow interconnections within computers to keep up with the advance of silicon information processing[7].

Even after the demonstration from Hirschman *et al.*, there is still some basic technological work to be done — to integrate emitters with the dominant form of silicon electronics (CMOS), for example. But the thrust of the new work towards integration with silicon electronics is well chosen. The benefit of silicon light-emission will probably be in cost-effective, integrated systems, possibly of surprising kinds. Examples could be displays, integrated optoisolators, low-density optical interconnections, or possibly radical applications such as microscopic sensor systems with built-in illuminators.

Certainly, this field is exciting, is progressing fast, and is dispelling doubts that the initially encouraging discoveries might turn to disappointment. There is increasing hope that the light at the end of the silicon tunnel is not an oncoming train. □

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MUSCULAR DYSTROPHY

Utrophin to the rescue

Kevin P. Campbell and Rachelle H. Crosbie

DUCHENNE muscular dystrophy (DMD) is a fatal genetic disease caused by the absence of dystrophin in muscle. The disease is characterized by the progressive loss of muscle strength, and patients usually die by their early twenties of respiratory or cardiac failure. Although great progress has been made in understanding the molecular genetics of DMD, no effective treatment for this devastating disease has yet been developed. Because dystrophin is a structural muscle protein, therapies for DMD will probably involve the replacement of dystrophin or the upregulation of a functionally related protein, such as utrophin. The paper by Kay Davies and colleagues on page 349 of this issue[1] shows for the first time that utrophin can effectively rescue dystrophin-deficient muscle *in vivo*, providing strong support for a therapeutic strategy to fight DMD involving the upregulation of utrophin.

Dystrophin is tightly associated with a large oligomeric complex of membrane glycoproteins that are collectively referred to as the dystrophin–glycoprotein complex (DGC; refs 2, 3). The DGC spans the sarcolemma of skeletal and cardiac muscle, and biochemical and molecular studies have shown that it provides an important structural link between the actin cytoskeleton and the extracellular matrix[2] (see Fig. 1). The involvement of this cytoskeleton–extracellular matrix connection in muscle physiology is not fully understood; however, it probably stabilizes the sarcolemma, thereby protecting it from stresses that develop during muscle contraction[4,5].

The absence of dystrophin in DMD patients results in several characteristic pathological features, including muscle-cell necrosis and regeneration[6], and elevated serum levels of muscle creatine kinase. At advanced stages of the disease, muscle is eventually replaced by fat and connective tissue. On the molecular level, the lack of dystrophin leads to a dramatic reduction in the levels of all of the other DGC components[2], and loss of the DGC breaks the transmembrane linkage and weakens the muscle-cell membrane. Elegant studies from the laboratory of Jeff Chamberlain[7,8] have shown that in the *mdx* mouse — a dystrophin-deficient animal model for DMD — restoration of the DGC by transgenic expression of dystrophin is necessary to rescue normal muscle physiology. In particular, the actin-binding and β-dystroglycan-binding domains are required[8]. These findings have been corroborated by the adenoviral expression of dystrophin and internally deleted forms of dystrophin (or minigenes) in *mdx* mice.

Utrophin is structurally similar to dystrophin[9], and it is mainly expressed at the neuromuscular junction in adult skeletal muscle (Fig. 1), although it is also found at the sarcolemma in fetal and regenerating muscle and, at very low levels, in DMD muscle[9]. Molecular studies of muscle from *mdx* mice have shown that utrophin associates with sarcolemmal glycoproteins to form a complex that is similar to the DGC (ref. 10), suggesting that utrophin can replace dystrophin at the sarcolemma in dystrophin-deficient muscle.

By expressing high levels of utrophin in *mdx* mice, Tinsley *et al.*[1] now demonstrate that utrophin can functionally replace dystrophin (Fig. 2). They show that overexpression of utrophin leads to the restoration of all of the components of the DGC, including the dystroglycan and sarcoglycan sub-complexes. Furthermore, serum creatine-kinase levels and muscle pathology also seem to be corrected, indicating that the restored complex is functional. Overexpression of utrophin even rescues the deterioration of the diaphragm, which is the most severely affected muscle group in the *mdx* mouse[11].

The results from the Davies group[1] provide the impetus for an exciting new avenue in DMD-therapy research — the identification of small molecules that increase the expression of utrophin in dystrophin-deficient skeletal muscle. These could be used to upregulate utrophin expression in all

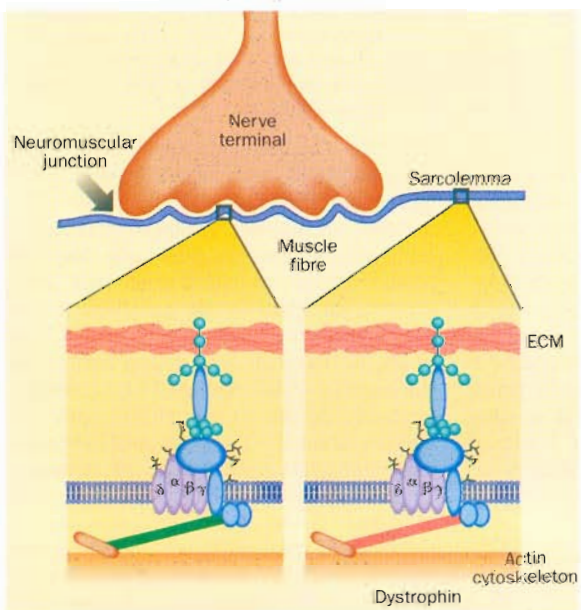

FIG. 1 Localization of dystrophin and utrophin in the muscle cell. The nerve terminal contacts the sarcolemma, creating the neuromuscular junction: expression of utrophin is confined to this region, whereas dystrophin is found throughout the sarcolemma. Both proteins are associated with a glycoprotein complex that binds to the extracellular matrix (ECM).

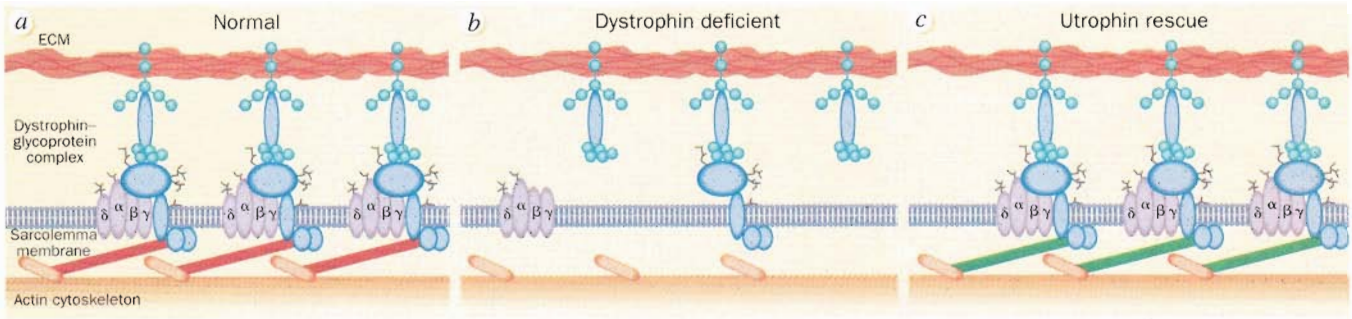

FIG. 2 A possible mechanism of utrophin rescue. *a*, Normal interactions of components of the dystrophin–glycoprotein complex with both the underlying actin cytoskeleton and the extracellular matrix (ECM). *b*, Disruption of the ECM–cytoskeleton linkage that occurs in the absence of dystrophin — as is the case in DMD patients and *mdx* mice. Levels of the dystrophin-associated proteins are also reduced in the absence of dystrophin. *c*, Utrophin, which is structurally similar to dystrophin, replaces dystrophin and restores the glycoprotein complex, maintaining the linkage between the intracellular cytoskeleton and the ECM.

muscles (including those responsible for respiration) and so alleviate completely the consequences of dystrophin deficiency in DMD patients. An advantage of this approach is that it does not require gene replacement, because the patients already have a functional utrophin gene. The next hurdle is to identify a drug that can induce utrophin expression; although this is a rather large obstacle, the upregulation of fetal haemoglobin in sickle-cell anaemia patients sets the precedent for such a therapeutic approach[12,13].

Tinsley *et al.*[1] also provide the first evidence to support the use of utrophin and utrophin-minigene transfer as a valid, therapeutic strategy. DMD patients do not express dystrophin, so their immune systems have not seen this protein. This increases the likelihood of an immune response to dystrophin that is expressed from an exogenous gene during dystrophin gene-replacement therapy. The use of utrophin as the transgene will minimize unwanted immunological responses, because utrophin is already expressed in DMD patients. For these types of therapies it will be important to determine the longevity of the utrophin rescue in the *mdx* mice.

There are now several lines to pursue in the development of treatments for DMD — dystrophin gene therapy, utrophin gene therapy and utrophin upregulation. A multifaceted approach to DMD therapy may well be the best course, and a better understanding of the function of the DGC will be invaluable for this. With regard to the use of utrophin upregulation as a therapeutic strategy for DMD, the next step will be to investigate the elements that control the expression of utrophin in skeletal muscle. For example, what regulates the localization of utrophin to the neuromuscular junction? By altering this regulation, could the expression of utrophin be extended to the sarcolemma? And because utrophin is expressed in the sarcolemma of fetal muscle, could the developmental regulation of utrophin be controlled? Although we don't yet understand the mechanisms controlling utrophin expression, it is possible to screen for small regulatory molecules in skeletal muscle cells. This may be a tremendous task, but it's too exciting a possibility to pass up.

Because the DGC and normal muscle physiology can be restored by the upregulation of a related protein, it may be possible to use a similar treatment for other types of muscular dystrophy (for example, limb-girdle and congenital) that are caused by primary defects in genes for other DGC components (such as the sarcoglycans and laminin-2)[2]. This depends on whether proteins that are functionally related to these components exist. Although the current results do not provide an immediate cure for DMD, they give us one more tool in an ever-growing arsenal with which to attack this devastating disease. □

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INTERSTELLAR CHEMISTRY

Missing link found in space

Stephen Lepp

AFTER more than 15 years of searching, H_3^+ has finally been detected in interstellar space. H_3^+ is the simplest stable polyatomic molecular ion, consisting of three bound hydrogen atoms minus one electron. Its characteristic absorption spectrum was detected by Geballe and Oka (who report on page 334 of this issue[1]), along two lines of sight towards young stars embedded in molecular clouds. This detection provides the most direct evidence yet for the ion–molecule reaction networks that are believed to drive the chemistry in interstellar molecular clouds. H_3^+ controls the entire chemistry of these clouds, and the chemistry in turn controls how fast the gas can cool and collapse to form stars[2]. So an understanding of the chemistry is critical to an understanding of star-forming regions.

Interstellar clouds are made mostly of molecular hydrogen (H_2), but traces have been found of nearly a hundred other molecular species[3]. These include familiar molecules such as water, carbon monoxide and ethyl alcohol, as well as many less familiar molecules, including radicals such as OH and CN. Although by number these molecules are a small fraction of the total, they dominate the cooling of the clouds, and are therefore important factors in forming new stars.

But these clouds are at very low temperatures, around 10 K, at which ordinary chemistry proceeds slowly or not at all. The chemistry must be driven instead by cosmic rays — high-energy particles that stream through the Galaxy and ionize the gas to form H_3^+. We believe that nearly all of the trace molecules are formed by reactions involving H_3^+, with the exception of molecular hydrogen, which is formed on grain surfaces.

H_3^+ is made after a hydrogen molecule is ionized by a cosmic ray to form the molecular ion H_2^+. This then reacts with molecular hydrogen to form H_3^+ and atomic hydrogen. H_3^+ controls the rest of the gas-phase chemistry and produces more com-