

Szent István Egyetem - Állatorvos-tudományi Kar

# Dystrophin and Utrophin

## The implications of similarity

2008/2009 tanév II. félév  
kurzusvezető: Dr. Kabai Péter

Szigetszentmiklós. 2009. május 1.

Készítette: Váradi Mihály  
IV. évfolyam, zoológia szak

**Abstract:** The largest known gene, DMD encodes several products of the dystrophin protein family. This review takes into account the structure of the isoforms, the origin of the DMD gene, the gene of utrophin, which seems to be an evolutionary duplicated version of DMD, which then moved to another chromosome, and the implications of the similarity between dystrophin and utrophin, such as a possible gene therapy approach to cure inherited diseases, like Duchenne muscular dystrophy, or fertility associated issues.

**Keywords:** dystrophin, utrophin, Duchenne muscular dystrophy

**Introduction:** The gene, which contains the information necessary for the production of every type of dystrophins, the DMD gene is the largest gene known so far in the human genom.

Mutations in the DMD gene may cause several diseases, the most well known –and researched- is the Duchenne muscular dystrophy, from which the name of the gene DMD originates. An evidence of the importance of dystrophin is that it can be found in nearly every taxa from *Coenorabditis elegans* to humans, and the basic structure is similar in every species, which indicates important functions. The aim of this review is to summarize what is known of dystrophin, utrophin -another similar protein-, and the possible use of utrophin as a method to cure patients in cases of the absence of dystrophin.

### **Dystrophin and its origin**

Dystrophin is the product of the DMD gene, the largest known gene in the human genom, consisting of approximately 2500 nucleotides (Koenig et al., 1988) found on the X chromosome. Dystrophin has several different isoforms, from the largest, found in muscle cells, which is the 427 kDa version, the smallest ones are the 71 kDa forms found in several non-muscle tissues, like sperm cells. The first product which has been discovered is the 427 kDa form, and the disease that the absence of it causes is the Duchenne muscular dystrophy. The main role of dystrophin is to serve as a connection between actin, with its N-terminal containing and actin binding, calponin homolog (CH) domain, and several membrane and transmembrane proteins, such as syntrophin, dystrobrevins and dystroglycans. Together they form the Dystrophin Associated Protein Complex, or DAPC (Yoshida and Ozawa, 1990; Ervasti and Campbell, 1991). All of the isoforms, from the 427 kDa to the 71 kDa show the similar basic structure, the main difference is that between these conservative domains, there is a number of spectrin-like repeats, and the number of these repeats differ in each isoform. Furthermore, in the 71 kDa isoforms, there is an alternate promoter, and because of this the CH domain is missing, instead if it is an unique N-terminus, its function is yet to be determined.

The DMD gene originates from before the vertebrates, a less sophisticated, but highly similar gene has been identified in *C. elegans*, and its product, a dystrophin related protein as well. The domain of this protein shows significant similarity, it has the CH domain, the C-terminal has the same domains, the main difference is the small number of spectrin repeats and two domains found only in this protein, with roles associated with DNA repairing and Chromosome segregation.

## **Utrophin, the twin of dystrophin**

In the human genome, there seems to be some genes that probably originated from the DMD gene with duplication. The largest and most complex gene related to DMD is the gene encoding utrophin (Wang et al., 1998; Roberts and Bobrow, 1998). It seems that during the evolution of vertebrates a large proportion of DMD has been duplicated, and moved to an autosomal chromosome from the X chromosome. The structure of the main product of the gene is utrophin, and as in dystrophin, there are several isoforms, with different functions. The CH domain, the spectrin like repeats, and the C-terminal with its cysteine-rich domains can all be found on utrophin, and this similarity could be used in cases of dystrophin shortage or absence, as an alternate curing method.

In recent studies conducted on mdx mice, which lack some, or all the isoforms (i.e. mdx<sup>3cv</sup> lacks every isoforms) it has been found, that in some cases, the lack of dystrophin indicates the upregulation of utrophin, which indicates that utrophin is not only similar in structure and function to dystrophin, but may even compensate it – more or less.

In mdx mice, normally the symptoms of Duchenne muscular dystrophy are rarely noticeable, however in double KO mdx mice, in which the utrophin gene is mutated as well, the symptoms are clearly visible. However, in human patients suffering from Duchenne, there seems to be no mutation in the utrophin gene, but unfortunately the upregulation seems to be insufficient. This may be, because though utrophin is similar, it is still a different protein, and so it can compensate, but only in a limited way.

However, this could mean, that if the upregulation could be enhanced, and the production of utrophin products would increase the symptoms may disappear.

## **Duchenne muscular dystrophy, and fertility**

A possible and promising option for the application of this knowledge is through gene therapy. There are two types of gene therapy, one modifying sperm cells or ovas, and the other modifying somatic cells. The latter would be the one most suitable for these kind of treatments. In these cases, patients suffering from the inherited diseases caused by the mutation of the DMD gene may be treated by plasmids containing modified genes responsible for the upregulation of utrophin. It is unlikely that a patient would lack both DMD and utrophin genes, and so it would be easier to increase the transcription from an otherwise working gene, then making a mutated one to work. There are of course methods for the latter approach as well, like antisense-mediated exon skipping, read-through of stop codons or administration of growth factors and the use of calpain inhibitors (K. E. Davies, 2007), but the gene therapy approach is in some ways more promising.

Supposedly the absence of the 71 kDa isoform of dystrophin results in abnormal flagellar morphology, which may decrease the fertility by as much as 50% (Hernández-González, E. O., 2005)

. It is still being researched, but if it would be found that it is so, then it should be monitored if utrophin compensates for this absence in sperm cells as well. If it does, then the gene therapy approach could be applied to these kind of fertility associated diseases as well.

## **Conclusion**

The similarity of dystrophin and utrophin is an important finding, and the implications of it are numerous. Diseases like the Duchenne muscular dystrophy, or fertility related issues may possibly be treated in an approach using utrophin to replace dystrophin.

However, there are limits the ability of utrophin in compensating dystrophin, and this should be noted when developing any kinds of treatments.

---

## References

Ervasti, J. M., (2007): Dystrophin, its interactions with other proteins, and implications for muscular dystrophy; *Biochim Biophys Acta.* 2007 1772(2):108-17

Hernández-González, E. O., (2005): Absence of Dp71 in mdx 3cv mouse spermatozoa alters flagellar morphology and the distribution of ion channels and nNOS; *Journal of Cell Science* 118, 137-145

John McC. Howell (1998): Is there a future for gene therapy?; *Neuromuscular Disorders* 9 (1999) 102–107

Dilair Baban, Kay E. Davies, (2007): Microarray analysis of mdx mice expressing high levels of utrophin: Therapeutic implications for dystrophin deficiency; *Neuromuscular Disorders* 18 (2008) 239–247

Sara Neumana, Alex Kabana, Talila Volkb, David Yaffea, Uri Nudel (2000): The dystrophin / utrophin homologues in *Drosophila* and in sea urchin; *Gene* 263 (2001) 17±29