Duchenne Muscular Dystrophy and Utrophin

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Duchenne muscular dystrophy (DMD) is one of the nine types of muscular dystrophies that affects about one out of every 3500 young males. Not only is it the most common type of muscular dystrophy in children, but it is also the most damaging. Its onset begins when the child is around 2 or 6 years old and usually severely weakens the person so that by the time they are between 20 and 30 years old, they are near death. As the disease is mainly a result of the presence of a mutant gene for the production of one of the main proteins in muscles, dystrophin, it rapidly weakens the muscles in the body so that by the time the child reaches adolescence, their ability to walk is severely impaired. The child is also prone to forms of mental retardation and poor motor skills.

Prior to the 21st century, much research was performed with intentions of developing a therapy and/or cure for DMD. Initially scientists looked into injecting greater amounts of dystrophin in the body in order to increase the amount of proteins in the muscles. Tests were performed on mice that had been engineered to have DMD and it was found, however, that as the level of dystrophin was already so low in the mice’s body, the body’s immune system considered the gene foreign, and thus rejected it. Further research was performed and by the year 2003, three main treatment procedures seemed fairly promising, one of which was the procedure of upregulating the gene, utrophin, in the body.

There are many reasons why utrophin is a good alternative to dystrophin. First of all, the two genes are considered naturally homologous, meaning they are structurally and functionally very similar. Secondly, utrophin is found in many of the body’s tissues as well as muscle, meaning it is very “well-known” by the body and has the capability to affect many parts of the body. In fact, the presence of utrophin in the muscle differs as the fetus develops. As an infant, utrophin is dispersed over much of the muscle, however once the child becomes a toddler, much of this utrophin is replaced by dystrophin, and then gradually as the muscle fully matures, utrophin is only present at the neuromuscular and myotendinous junctions of the body. Lastly, the structure of the two natural genes allows for utrophin to behave in fairly the same manner as dystrophin in the muscles.

The figure below shows four dystrophin genes that do not cause DMD, the first one being the most common in a person without the disease. As a result of much mice testing, (portrayed by the middle two genes), scientists were able to discover that the size of both the N-terminal (red) and the dystrophin portion of the gene (yellow) were important to preventing the disease but in no means essential. On the contrary, “deletions in the cysteine-rich domain” (green) were a significant cause of DMD. The C-terminal (blue), although its presence is definitely required, can be significantly shorter if the patterns of its divisions are correct. However, if these patterns are incorrect, the mice tended to carry the phenotype for Becker muscular dystrophy. Although this is a much less intense form of muscular dystrophy than DMD, it still results in muscle weakness and a shorter life expectancy. The last gene shown in the figure is a healthy gene that would be present if utrophin were to be injected into the neuromuscular and myotendinous junctions of a person’s muscles who suffers from DMD. Note the natural similarities to the other three healthy dystrophin genes, most importantly the first gene.

The idea of injecting utrophin into the muscles of the human body in order to treat DMD is still very novel. However, according to an article published in October 2008 by Science News, researchers at the University of Minnesota medical school have been able to inject utrophin with the “cell-penetrating tag TAT” into the leg muscles of a dog and see widespread effects of strengthened muscles in the body. This is significant because prior to this discovery, utrophin had only been injected into mice and shown to have widespread effects. A dog is said to be only nine times smaller than a human, indicating that research on ways to treat DMD in humans is progressing. As of right now, no human tests have been performed, however there are promising hopes that in the future utrophin will be used as a treatment for DMD in humans. According to scientists, research is being done on how to develop a pill that will administer the appropriate amount of utrophin to the person’s muscles at regulated intervals. The pill would have to be taken “on a regular basis” and would only treat the disease. As far as finding a cure for DMD, scientists are still researching various procedures.

REFERENCES