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Weizmann Institute scientists discover:

A KEY PLAYER IN EMBRYONIC MUSCLE DEVELOPMENT

In the future, this finding may help in designing new methods for healing injured and diseased muscle tissue using stem cells

Muscle fibers are large cells that contain many nuclei. They begin, like all animal cells, as naïve embryonic cells. These cells differentiate, producing intermediate cells called myoblasts that are now destined to become muscle. New myoblasts then seek out other myoblasts, and when they find each other, they stick together like best friends. In the final stage of muscle fiber development, the cell membranes of attached myoblasts open up and fuse together, forming one large, unified cell.

How myoblasts identify other myoblasts and how they cling together had been established, but the way that the cell membranes fuse into one has remained a mystery. Now, a study by Weizmann Institute scientists has shed light on this mystery. The study was carried out by research student Rada Massarwa and lab technician Shari Carmon under the guidance of Dr. Eyal Schejter and Prof. Ben-Zion Shilo of the Institute’s Molecular Genetics Department, with help from Dr. Vera Shinder of the Electron Microscopy Unit. The cells’ system for identifying other myoblasts and sticking to them consists of protein molecules that poke through the outer cell membrane – one end pointing out and the other extending into the body of the cell. These recognition proteins anchor the cells together, but what makes myoblasts open their doors to each other and merge into one cell?

The scientists discovered that a protein called WIP, which attaches to the internal part of the myoblast recognition protein, plays a key role in muscle cell fusion. WIP communicates between the recognition protein and the cell’s internal skeleton, which is made of tough, elastic fibers composed of a protein called actin. The skeletal actin applies force to the abutting cell membranes, opening and enlarging holes that allow the cells to merge. The Weizmann Institute team found that the WIP protein is activated by an external signal once myoblasts identify and attach to each other. Only when it receives this signal does WIP hook the actin fibers in the skeleton up to the myoblast recognition protein, allowing cell fusion to proceed.

The WIP protein has been conserved evolutionarily. In other words, versions of it exist in all animals, from microorganisms such as yeast, through worms and flies, and up to humans. This means that the protein fulfills a function necessary for life but also, say the scientists, because of this

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conservation, studies conducted on this protein in fruit flies can teach us quite a bit about how it works in humans.

To further examine the role of WIP, the scientists knocked out the gene responsible for producing it in fruit flies. In flies that did not make the protein, normal muscle fibers were not produced. WIP-deficient myoblasts continued to identify and cozy up to one another, but fusion between cell membranes did not take place, and multi-nucleated muscle fibers failed to form. An article describing these findings appeared today in the journal Developmental Cell.

This study, which improves our understanding of the process of muscle formation, may assist in the future, in devising new and advanced methods for healing muscle. Specifically, these might include ways of fusing stem cells with injured or degenerated muscle fibers.

Fusion between cell membranes plays a key role in development of different kinds of bone cells, placental cells and immune system cells, as well as in fertilization and in the penetration of viruses into living cells. Understanding how membrane fusion takes place may one day lead to the development of ways to encourage the process when it’s needed or hinder it when it’s likely to cause harm.

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Prof. Shilo is the incumbent of the Hilda and Cecil Lewis Professorial Chair in Molecular Genetics.