A better molecular understanding of myotubular myopathy

Tiny deviations in the cells can sometimes have severe consequences. Researchers have discovered why cells from patients with the rare muscular disease myotubular myopathy cannot function properly. Through the article published in *Nature,* it has become clear how a dynamic cellular process is regulated by means of minute changes of certain membrane lipids and altered in this muscle disease.

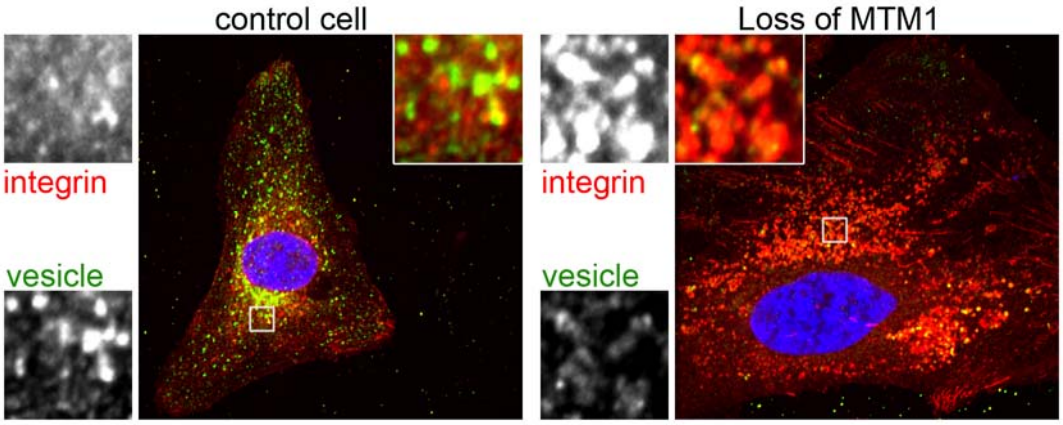

Figure 1: Accumulation of integrin (red), an important component of muscles, in vesicles (green) from cells without MTM1 (right images including magnified view) or from control cells (left images including magnified view).

The group of Volker Haucke from the Leibniz-Institut für Molekulare Pharmakologie in Berlin (FMP), in collaboration with the laboratories of Jocelyn Laporte from IGBMC in Strasbourg and Carsten Schultz at the European Molecular Biology Laboratory (EMBL) in Heidelberg, has been researching what goes wrong in this disease at the molecular level – and has now come across a general organisational principle of cells.

Up to now, it has been known that this hereditary disease involves a defect in the gene *MTM1*, as a result of which muscle fibres do not function normally. The gene produces an enzyme that is specialised in cleaving phosphate groups from the heads of certain membrane lipids called phosphoinositide phosphates (PIPs). PIPs are used by the cell to tag its compartments and to regulate the transport of substances. "The cell is a very dynamic system, which one can imagine as a metropolis in which buses move in many directions" explains Volker Haucke. "The final destination is indicated on the bus and can be changed depending on its present direction. In a similar manner, the compartments and transport containers within cells are constantly putting on different PIPs as tags and thus change their identity." Each PIP consists of a fat-soluble tail that is anchored in the membranes of the cell compartments, and a water-soluble head that protrudes from the membrane. The head can be loaded with phosphates at different sites, the phosphate groups are added or detached by enzymes. This is a minimal change that takes place in a flash, yet it is unmistakably read by the cell. Thus, for example, if a phosphate group tags a certain position, it is a message for the cell that this specific container should be transported into the interior of the cell; if the lipid tag is different, the container migrates to the outer cell membrane, docks there and unloads its freight to the outside.

This kind of transport comes to a halt in myotubular myopathy, as could be shown by Katharina Ketel from the Haucke group with intricate experiments and high-resolution images from inside the cell. This clarifies

how dynamic processes in a cell are directed and illustrates how studying a rare genetic disease can discover an essential molecular mechanism for our cells to function properly. "In healthy cells, phosphate groups are never randomly removed from PIPs, because a cell compartment would then suddenly be left without an identity – that would be equivalent to a loss of memory. The compartment would no longer know where it's from and where it's supposed to go," explains Volker Haucke.

"In myotubular myopathy patients, some of the containers that were originally supposed to transport proteins to the cell surface get stranded inside the cell because the tag is lost," says Jocelyn Laporte, a contributor to the work studying this disease since 22 years. "In muscles, this may mean that proteins necessary for the formation of muscles, their integrity and function do not get to the right place." In their experiments in cell culture, the Berlin researchers were able to rescue the tagging of containers with PIPs synthesized by the Schultz group. “By adding lipids with the proper code, their identity can be rescued”, explains Carsten Schultz. This might be a starting point to envisage the development of novel drugs for treating myotubular myopathy.

Reference:

A phosphoinositide conversion mechanism for exit from endosomes. Katharina Ketel, Michael Krauss, Anne-Sophie Nicot, Dmytro Puchkov, Marnix Wieffer, Rainer Müller, Devaraj Subramanian, Carsten Schultz, Jocelyn Laporte, Volker Haucke. Nature 2016 doi:10.1038/nature16516

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