MicroRNAs regulate the formation of mitochondria in cells

April 9 2018

Muscles require a large amount of energy to function. This is provided primarily by mitochondria in cells that consume a lot of energy. We therefore find more of these powerhouses of the cell in muscle cells than in other cell types with a lower metabolic rate. Scientists at the Max Planck Institute for Heart and Lung Research in Bad Nauheim have now identified a mechanism that can be used to regulate the development of mitochondria in muscle cells. This is what makes the endurance capacity of muscles even possible in the first place.

Energy is supplied to cells via two different mechanisms: by means of a process known as glycolysis, cells extract the energy carrier adenosine triphosphate (ATP) from glucose. Oxygen is not required. The disadvantage of glycolysis is its low efficiency. For this reason, cells that require a lot of energy to function manufacture ATP primarily via the respiratory chain. This is more efficient than glycolysis. It takes place in the mitochondria and consumes oxygen. Due to their relatively high energy demand, muscle cells require a particularly high number of mitochondria compared to other cell types.

Scientists in Thomas Braun's "Cardiac Development and Remodelling" Department have now discovered a mechanism that controls the formation of mitochondria during muscle stem cell differentiation into functional muscle cells. Short, non-coding RNA molecules, known as microRNAs, play a crucial role in this process, as a does a group of genes known as a mega gene cluster. Thomas Böttger, Group Leader in the Department at the Max Planck Institute explains how it works: "In

stem cells, the Dlk1-Dio3 gene cluster blocks the formation of mitochondria. This retains the carefully orchestrated balance of energy metabolism in these cells."

New mitochondria for muscle cells

If stem cells develop into muscle cells, the energy demand changes dramatically. A large number of mitochondria are formed within a short space of time. "We were able to show that the mega gene cluster is active in stem cells but not in any of the differentiated somatic cells that we studied," says Böttger. The Max Planck researchers concluded from this that the mega gene cluster is switched off during cell differentiation.

Evidence of the underlying mechanism emerged when the scientists studied in greater depth the differentiation of stem cells into muscle cells: "In parallel with the slow-down in the Dlk1-Dio3 gene cluster, we noted an increase in two non-coding microRNAs, namely miR-1 and miR-133a," says Böttger. When miR-1 and miR-133a were switched off in the muscle cells in the experiment, the individual components of the mega gene cluster could be shown in these cells. "This is a strong indication that miR-1 and miR-133a prevent the formation of the mega gene cluster," says Böttger. "If both microRNAs are absent, the mega gene cluster remains active. In fact, we then observed a decrease in mitochondrial genes and atypical mitochondria."

Studies on mice in which the genes for miR-1 and miR-133a were genetically knocked out confirmed the data: "Significantly fewer mitochondria were found in the muscle cells of miR-1/miR-133a knockout mice compared to the muscle cells of the control animals. While maintaining the same strength, we noted a significantly reduced endurance capacity among the knockout mice," says Böttger.

The researchers' proposed the following explanation for this

phenomenon: while the energy for short-term muscle activity is provided anaerobically via glycolysis, aerobic processes are required for endurance. "The muscles need sufficient mitochondria for sustained muscle activity," says Böttger. "Our study shows that the two microRNAs – miR-1/miR-133a – deactivate the mega gene cluster during the formation of muscle cells from stem cells and as a result the formation of large numbers of mitochondria is possible." The study thus makes an important contribution to understanding the transformation of stem cells into somatic cells.

More information: Stas Wüst et al. Metabolic Maturation during Muscle Stem Cell Differentiation Is Achieved by miR-1/133a -Mediated Inhibition of the Dlk1-Dio3 Mega Gene Cluster, *Cell Metabolism* (2018). DOI: 10.1016/j.cmet.2018.02.022

Provided by Max Planck Society