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ALS skin fibroblasts reveal oxidative stress and ERK1/2-mediated cytoplasmic localization of TDP-43

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Amyotrophic lateral sclerosis (ALS) is a devastating disease which leads to death of motor neurons (MNs). There are many genetic causes leading to ALS, one of which is represented by mutations in an important protein called TAR DNA binding protein (TDP-43). In a healthy individual, the TDP-43 protein can be found in a compartment of MNs called the nucleus, which acts as a command centre. However, in some patients with ALS, TDP-43 is moved out of the nucleus and into the cytoplasm, a jelly-like material which surrounds the nucleus. The movement of TDP-43 is thought to lead to a series of changes within the MNs which damage and lead to their death. However, many of these changes are still not fully understood.

Previously, many studies have used cellular lines to try to reproduce the mislocalization of TDP-43 in order to study its connection to MN death. However, there are major limitations to using cell lines in ALS research, one of them being their limited availability. In the study by Romano et al., (2020), the researchers took skin biopsies from patients with ALS with mutations in TDP-43, patients with ALS without TDP-43 mutations and healthy individuals (control group) and used them to grow a type of skin cell called fibroblasts. After comparing the fibroblasts from all participant groups, the results show that in the ALS groups, fibroblasts were unable to produce energy and had a decreased ability to survive. These changes were not observed in the control group. High levels of oxidative stress were also measured in skin fibroblasts from ALS patients, indicating that these cells have and reduced capacity to remove some of the harmful substances that result from their activity. Moreover, when they experimentally decreased the activity of signal-regulated kinases (ERK1/2), a molecule which controls the development and multiplication of cells, the results showed that the movement of TDP-43 to the cytoplasm was reduced in ALS fibroblasts.

Taken together, these results indicate that fibroblasts from ALS patients exhibit similar cellular defects to those previously observed in the MNs of ALS patients, and that they can be used as an alternative model for understanding the mechanisms of ALS development and progression. Moreover, the findings of this study also point towards a connection between the signalling proteins ERK1/2 and toxic cytoplasmic accumulation of TDP-43, suggesting that ERK1/2 could be used as a potential target for therapeutic strategies. develop treatments.