Research discovers inhibitor to reverse toxic DUX4 effects

11 September 2019

Credit: CC0 Public Domain

About one in 8,000 people have facioscapulohumeral muscular dystrophy, according to a 2014 study, which is relatively common in the world of genetic diseases. New University of Minnesota Medical School research identifies an inhibitor that protects cells from toxic effects associated with this disease in cells and mice.

Facioscapulohumeral muscular dystrophy (FSHD) is a genetic disease that affects the muscles in the face, upper body, abdomen, and back, and can be extremely debilitating. It is caused by the misexpression of a gene called DUX4. The pathophysiology of FSHD is not yet understood, but it is known that people who get the disease have a mutation that leads to the DUX4 gene being expressed when it should be off. The gene codes for a protein that is an important central regulator to the function of the cell because it controls other genes. Therefore, when DUX4 gets misexpressed, the protein activates other genes that also shouldn't be expressed, and the cell ultimately stops functioning properly, which leads to FSHD.

In a study published in *Science Advances*, Michael Kyba, Ph.D., and Darko Bosnakovski, DVM, Ph.D., both researchers in the Department of Pediatrics at the U of M Medical School, and their team discovered a way to deactivate DUX4 and take away the toxic effects in cells, as well as in a mouse model for FSHD.

Kyba had previously found that DUX4 turns on target genes by bringing in an enzyme called p300 to certain genes, where it then adds chemical modification to all of the histones around that gene. As the most abundant proteins in the nucleus of a cell, histones regulate the function of the DNA. The chemical modification to the histones opens up the gene and allows it to be expressed at a high level when it would normally never be expressed in the muscle.

Kyba's new research tested a compound that was newly synthesized by Medicinal Chemists Michael Walters at UMN and Ajit Jadhav at the National Institutes of Health (NIH), due to its potential to block p300. Kyba tested this compound in a mouse model for FSHD and found that the compound called iP300w was effective in blocking the p300 enzyme needed by DUX4. Therefore, DUX4 did not have the resources to perform its job, and cells were protected from its toxic effects.

Drug companies are currently researching ways to turn the DUX4 gene off, but Kyba's findings are the first to show that the disease can be treated by blocking the activity of the DUX4 protein, even after it is already expressed.

"Whether this drug will be tested in patients will

require additional study. The p300 enzyme functions in other situations, therefore blocking it in all cells may have side effects," said Kyba. "In the case that such side effects should be significant, we are also actively searching for a drug that interferes with the ability of DUX4 to recognize p300, which would allow p300 to continue functioning normally in its other roles."

More information: "A novel P300 inhibitor reverses DUX4-mediated global histone H3 hyperacetylation, target gene expression, and cell death" *Science Advances* (2019). DOI: 10.1126/sciadv.aaw7781 , advances.sciencemag.org/content/5/9/eaaw7781

Provided by University of Minnesota