

Novel therapeutic options for spinal muscular atrophy by unraveling the cellular mechanism of SMA

Spinal muscular atrophy (SMA) is the most common genetic cause of death in childhood. About 30,000 people with SMA are currently living in Europe and the US. In about half of the individuals with SMA, the disease causes death within the first two years of life. So far, there is no cure for SMA. The research group led by Professor Wirth at the Institute of Human Genetics at the University Hospital of Cologne succeeded in discovering a cellular mechanism of SMA. The results were published in the prestigious scientific magazine The American Journal of Human Genetics.

Spinal muscular atrophy (SMA) leads to degeneration of the motor neurons in the spinal cord that are responsible for movement in the body. The molecular cause of this disease is the loss of the SMN1 gene, resulting in the death of motor neurons. The SMN1 gene is the basis for the production of the SMN protein. This is a vital protein and is found in all our cells. Motor neurons require a great deal of this protein - 50 times more than any other cell.

Motor neurons are unique cells: their cell bodies are located in the spinal cord, from which a long process of over 1 m – the so called axon- is extending. This connects with the muscle through the largest synapse in our body, the so called neuromuscular junction – to stimulate muscle and allow contraction. Precisely this part is disrupted in SMA. However, the exact cellular mechanism behind is not yet understood.

Since SMN is an essential protein, the question of why motor neurons are particularly affected by the loss of SMN was still elusive. To answer this question, the research group of Professor Wirth made use of a unique observation. In rare cases, some SMA family members remain fully asymptomatic, despite carrying the same SMN1 mutations and the same number of SMN2 copies as their affected family members. The researchers hypothesized that these people carry modifying genes in their genome that protect against the disease. Few years ago, Prof. Wirth and her group identified Plastin 3 (PLS3) as the only SMA protective modifier so far. The protective gene PLS3 and an interacting partner of PLS3 - Coronin 1C (CORO1C) - have led the group to uncover the cellular mechanism of the disease.

Seyyedmohsen Hosseinibarkooie, postdoc in Wirth's lab, has shown that small amounts of SMN result in impaired endocytosis - a process essential for the uptake and transfer of solid or liquid particles in a cell, including certain pathogens. This malfunction can be restored by PLS3 or CORO1C. By endocytosis not only the neurotransmitter acetylcholine but also other important molecules are incorporated in the motor neuron. The endocytosis is essential for motor neurons and is supported by various types of endocytosis.

The PhD student Miriam Peters used a combined therapy in severely affected SMA mice - small amounts of SMN-antisense oligonucleotides (ASOs) together with PLS3 overexpression - to rescue SMA: Animals survived >250 days instead of only 14 days. This situation can be compared with the severely affected type I SMA individuals, where ASO therapy allows a slight increase of SMN, but not sufficient to cure these people. Combined therapy with a second agent that increases PLS3, endocytosis or F-actin could constitute a long-term therapeutic option for the treatment of people with SMA.

"The scientific findings from this research could be also important for other neurodegenerative diseases such as Alzheimer's, Parkinson, ataxia, hereditary sensory motoneuropathy (CMT2) and amyotrophic lateral sclerosis (ALS) represent," said the head of the working group of Prof. Brunhilde Wirth.

Hosseinibarkooie SM*, Peters M*, Torres-Benito L, Rastetter RH, Hupperich K, Hoffmann A, Mendoza-Ferreira N, Kaczmarek A, Janzen E, Milbradt J, Lamkemeyer T, Rigo F, Bennett F, Guschlbauer C, Büschges A Hammerschmidt M, Riessland M, Kye MJ, Wirth B. The power of human protective modifiers: PLS3 and CORO1C unravel impaired endocytosis in spinal muscular atrophy and rescue SMA phenotype.

Am J Hum Genet. 2016, DOI; <http://dx.doi.org/10.1016/j.ajhg.2016.07.014>

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[http://www.cell.com/ajhg/abstract/S0002-9297\(16\)30288-9](http://www.cell.com/ajhg/abstract/S0002-9297(16)30288-9)

Translation from the original text of Christoph Wanko (in German)