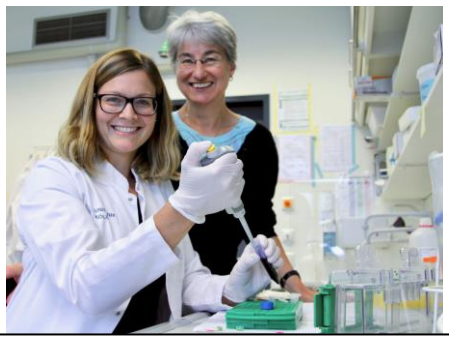
Press release:

CHP1: a novel protective gene for spinal muscular atrophy (SMA) - opens new therapeutic options

The research group of Prof. Dr. Brunhilde Wirth, Head of the Institute of Human Genetics at the University Hospital Cologne, succeeded to identify calcineurin-like EF-hand Protein 1 (CHP1) reduction as a novel protective modifier for the detrimental neurodegenerative disorder spinal muscular atrophy (SMA). The results of this study have been published 28.06.2018 in *Brain*, an international highly renowned journal.



Eva Janzen, PhD student in the Wirth lab and Prof. Dr. Brunhilde Wirth, Director of the Institute of Human Genetics University of Cologne, Photo: Uniklinik Köln

SMA is the second most frequent autosomal recessive inherited disease and the leading genetic cause of infant lethality. The carrier frequency in the European population is 1:35. About 30,000 individuals are affected by SMA in Europe and the USA, whereas about 60% of the affected individuals develop the most severe form of SMA resulting in early lethality.

On molecular level SMA is caused by the loss of the *SMN1* gene, which encodes for the SMN protein. The SMN protein has essential functions in all cells for our body. However, SMN is in particular important for the survival of motor neurons, the neurons innervating the muscle and thereby inducing muscle contraction.

A major disease hallmark is the progressive loss of motor neurons, eventually leading to muscle atrophy and weakness. An early pathological feature of SMA is the reduced size and maturation of the neuromuscular junction (NMJ), the synapse connecting motor neuron and muscle fibre and thereby essential for neuronal signal transmission to the muscle. However, in the most severe form also further organ dysfunctions were described.

In previous studies, Prof. Wirth and her research group identified plastin 3 (PLS3 as a protective genetic modifier in humans, who remained unaffected, despite carrying the genetic predisposition for SMA. Eva Janzen, PhD student in the Wirth laboratory together with Natalia Mendoza-Ferreira and Seyyedmohsen Hosseinibarkooie, PhD student and Postdoc in the Wirth laboratory, respectively, identified CHP1 as a novel PLS3 interacting partner and were able to proof the beneficial effect of CHP1 reduction in various SMA models.

Recently, the first therapy for SMA patients with Spinraza^{TM} was approved by the FDA and EMA. Spinraza^{TM} is an antisense oligonucleotide (ASO) able to increase SMN levels. Nonetheless, in severely-affected type I SMA patients it seems to be insufficient to fully rescue the disease. Therefore, a second SMN-independent compound supporting the SMN-dependent therapy is a highly promising therapeutic approach. In order to resemble the situation of Spinraza^{TM} -treated severely affected SMA

patients, severely-affected SMA mice were injected with a suboptimal dose of ASO resulting in doubling the life expectancy. Additional CHP1 reduction in combination with Spinraza™ further prolonged the survival by 1.6-fold and improved the main disease hallmarks of SMA.

The additional beneficial effect of CHP1 reduction was traced back to the activation of the enzyme calcineurin, resulting in increased neuronal endocytosis. Endocytosis is an essential process for all cell of the body, but particularly relevant at neuromuscular synapses to recycle the neurotransmitter acetylcholine. Moreover the scientists showed for the first time that calcineurin activity is diminished in SMA cells and thereby most likely contributes to the reduced endocytosis in SMA.

Taken together, the scientists showed that CHP1 reduction is a novel protective modifier for SMA supporting the Spinraza™ therapy. Thus, for the future CHP1 reduction is a highly attractive therapeutic intervention for SMA patients in combination with ASO treatment.

Original publication

Janzen E, Mendoza-Ferreira N, Hosseinibarkooie S, Schneider S, Hupperich K, Tschanz T, Grysko V, Riessland M, Hammerschmidt M, Rigo F, Bennett CF, Kye MJ, Torres-Benito L, Wirth B.

CHP1 reduction ameliorates spinal muscular atrophy pathology by restoring calcineurin activity and endocytosis.

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