Fucosidosis – present knowledge and future prospects

Fucosidosis is an autosomal recessive storage disorder caused by the defect of the enzyme alpha-fucosidase. The FUCA1 gene, that codes for α-fucosidase, is located on chromosome 1. Clinically, fucosidosis is characterized by neurodegeneration with progressive mental and motor deterioration. Further clinical signs include dysmorphic face, gingival hypertrophy, angiokeratoma, enlarged liver and spleen, eye abnormalities and hearing loss. MRI examination of the CNS reveals a generalized hypomyelination of white matter tracks. In the past, two phenotypes had been distinguished: A severe infantile form, designated type I, and a milder form, referred to as type II. But this classification seems to be arbitrary, as studies of a large number of patients have shown that type I and II rather represent the extremes of a continuous clinical spectrum.

Nowadays, besides palliative care for the treatment or alleviation of symptoms, bone marrow transplantation is the only therapeutic option for patients affected by fucosidosis. The benefit of this procedure, however, is limited by the fact that the disease progression is very fast and cellular and tissue damage cannot be rescued by the transplantated cells. There exist animal models of fucosidosis that allow the evaluation of new therapeutic interventions. An ex-vivo gene therapy experiment was performed in a canine model whereby a retroviral gene transfer into autologous hematopoietic stem cells was used. But this procedure was unsuccessful, as graft failure occurred in all transplants.[1]

In order to overcome the blood-brain barrier, recombinant fucosidase was applied intracisternally to young affected dogs. After three monthly injections an increase of enzyme activity and a decrease of oligosaccharide storage could be demonstrated in all brain areas.[2] Although this procedure was safe and well-tolerated, it remains questionable whether it can ever be used also in humans.

An analysis of the fucosidase gene revealed 22 different gene alterations, including 4 missense mutations and 18 nonsense mutations, that consisted of 7 stop-codon mutations and 11 other complex changes.[3] Stop-codon mutations lead to premature translation termination and to the synthesis of a non-functional enzyme. It is known that the drug gentamicin is able to induce the so-called "read-through" of premature stop-codons and to restore production of full-length proteins with normal enzymatic activity.[4] This therapeutic principle has been applied in cell culture systems, in an animal model of mucopolysaccharidosis type I and in a clinical trial in Duchenne muscular dystrophy patients, whereby newly designed drugs were used that are less toxic than gentamicin. The "read-through" method seems to be a promising therapeutic approach, but of course is suitable only for patients who carry a stop-codon mutation.

As it has often been shown that early treatment is necessary to prevent irreversible organ damage, newborn screening has been or will be established in many countries. In the future it can be expected that more effective therapies, for example gene therapy, personalized medicine such as read-through drugs, and early initiation of treatment may change the prospect for fucosidase patients.

Literature

1. Ferrara ML, Occhiodoro T, Fuller M, et al. Canine fucosidosis: a model for retroviral gene transfer into haematopoietic stem cells. *Neuromuscul Disord*. 1997;7:361-366.
2. Kondagari GS, King BM, Thomson PC, et al. Treatment of canine fucosidosis by intracisternal enzyme infusion. *Exp Neurol*. 2011;230:218-226.
3. Willems PJ, Seo HC, Coucke P, et al. Spectrum of mutations in fucosidosis. *Eur J Hum Genet*. 1999;7:60-67.
4. Keeling KM, Xue X, Gunn G, et al. Therapeutics based on stop codon readthrough. *Annu Rev Genomics Hum Genet*. 2014;15:371-394.

Prof. Dr. M. Beck
Institute of Human Genetics
University of Mainz, Germany