THE CHOLESTEROL METABOLISM AS TREATMENT TARGET FOR MJD

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**ABSTRACT:**

Machado-Joseph disease (MJD), also known as Spinocerebellar ataxia type 3 (SCA3), is the most prevalent autosomal dominant spinocerebellar ataxia worldwide. It is caused by an expansion of a CAG repeat in the *ATXN3* gene leading to a polyglutamine expansion in the encoded Ataxin-3 protein. MJD thus belongs to the group of polyglutamine (PolyQ) diseases. A hallmark of SCA3 and other polyglutamine diseases is the formation of neuronal intranuclear inclusion bodies, as well as neurodegeneration in characteristic brain areas. To date, no approved treatment strategy is available for MJD patients.

Cholesterol plays a critical role in the physiology of neurons, from their development until adulthood and it is required to maintain synaptic activity between neurons. Defects in the metabolism of brain cholesterol have been demonstrated to contribute to several neurodegenerative diseases, including Alzheimer’s disease (AD), Parkinson’s disease (PD) and Huntington’s disease (HD). The synthesis of brain cholesterol occurs almost exclusively within the brain itself and an excess of cholesterol might be detrimental to neurons. However, the brain is incapable of eliminating cholesterol due to its inability to cross the blood-brain-barrier. For its elimination from the brain, Cholesterol must be converted into 24S-hydroxycholesterol (24S-OH-Chol), which can cross the blood-brain barrier.

This study proposes that a therapeutic strategy targeting the cholesterol metabolism and, by extension, cholesterol levels within the brain, holds promise for the treatment of MJD. Following the demonstration of disturbances in Cholesterol metabolism in a transgenic mouse model of MJD, a gene therapy-based approach was employed to specifically modify brain cholesterol levels by targeting a gene responsible for cholesterol turnover in the brain. We then studied the efficacy of this treatment on MJD-associated symptoms in our mouse model. Moreover, we demonstrate in MJD patients that genetic modifications within the Cholesterol pathway may contribute to the disease.

We believe that our results will enhance our understanding of the pathogenic processes underlying MJD and represent a significant contribution to the development of effective therapeutic interventions for this condition.