Novel function of ATXN7 in cilia and impact on the SCA7 pathogenesis

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Principal Investigators

TROTTIER Yvon

Institution

IGBMC Strasbourg

Contact information of lead PI

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Research Abstract

The general aim of Ciliataxia is to determine the contribution of cilia dysfunctions in the pathogenesis of SpinoCerebellar Ataxia 7 (SCA7). SCA7 belongs to polyglutamine (polyQ) disorders that include 5 other SCAs, and to the large group of dominant cerebellar ataxias. SCA7 causes degeneration of cerebellar neurons and photoreceptors, leading to ataxia and blindness, respectively.

Cumulative evidence indicates that toxic gain of function of mutant proteins and loss of normal protein function account for PolyQ pathogenesis. The ATXN7 involved in SCA7 has a known transcriptional function in the nucleus. Transcriptional alterations are observed in SCA7, however, the underlying mechanism remains controversial. A recent study indicates that

transcriptional defects are likely not the only pathomechanism of the disease.
Besides the nucleus, ATXN7 naturally localizes in the cytoplasm of neurons, where its function is unknown. Partner 1 of Ciliataxia, who is studying SCA7 pathology for 15 years, recently uncovered the localization of ATXN7 in cilia. Through their collaboration, partner 2, who is studying the role of cilia in the embryogenesis of zebrafish, provided evidence that ATXN7 loss of function causes a large spectrum of ciliary phenotypes in fish, suggesting a new function of ATXN7 in cilia. It is noteworthy that ATXN7 would be the third SCA protein, with SCA10 and SCA11, to show a ciliary function, suggesting that common cilia dysfunction may contribute to disease processes. Along this line, our current analysis has revealed a depletion of wtATXN7 from photoreceptor cilia correlating with the initiation of SCA7 mouse retinopathy. Therefore, we have hypothesized that polyQ expansion causes dysfunctions of ciliary ATXN7 resulting in defective cilia that contribute to neuronal degeneration in SCA7.
The first important issue of Ciliataxia is thus to determine the ciliary function of ATXN7 to subsequently understand the consequence of its dysfunction in SCA7. The Objective 1 aims at determining the spectrum of ciliary functions of ATXN7 by identifying in which type of cilia and in which type of ciliated cells or tissues ATXN7 could play a role. To this end, we will combine the characterization of ATXN7 loss of function in zebrafish, a dedicated system to study ciliary defects, and in systematic or conditional knockout mice. The Objective 2 aims at understanding the molecular function of ciliary ATXN7 and identifying modifiers of ATXN7 loss of function.
The second issue is to analyzing the toxic effect of polyQ expansion on the ciliary function of ATXN7 and on the functional and structural integrity of cilia in SCA7 pathology. The Objective 3 aims at developing and characterizing a SCA7 transgenic zebrafish model in order to understand how polyglutamine expansion toxicity could alter ATXN7 ciliary functions and lead to ciliary defects during development and adulthood. The Objective 4 aims at carefully characterizing the previously observed defects of photoreceptor cilia and depletion of ciliary ATXN7 in correlation with the development of SCA7 mouse retinopathy. Furthermore, we will analyze the structural and functional integrity of cilia in other types of cells and tissues affected in SCA7, with specific attention to the cerebellar neurons.
The last, and the most crucial issue is to understanding the specific contribution of ATXN7 ciliary depletion and the resulting ciliary defects to SCA7 pathogenesis. In the Objective 5, we will use genetic strategies to test if restoring the level of wtATXN7 in the cytoplasm provides protective effect on the pathology of SCA7 zebrafish and on the retinopathy of SCA7 mice.
The original partnership of Ciliataxia offers a powerful workflow where zebrafish results build the groundwork for mouse studies. The success of Ciliataxia will provide a better understanding of the pathomechanisms underlying polyQ disorders and, possibly, other dominant cerebellar ataxias

Further information available at:

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