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LECTURE

Nuclear localization and transport: a critical pathomechanism in Machado-Joseph disease

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Abstract

Machado-Joseph disease (MJD) or Spinocerebellar ataxia type 3 (SCA3) is caused by a polyglutamine expansion in the ataxin-3 protein. In controls, ataxin-3 is predominantly located in the cytoplasm but forms protein aggregates in the nucleus of neurons in MJD/SCA3 patients. We recently demonstrated in vivo that the toxicity of expanded ataxin-3 is linked to its intracellular localization: Targeting ataxin-3 to the nucleus gave rise to a strong phenotype with a high number of protein aggregates. Purely cytoplasmic ataxin-3, however, even with a highly expanded polyglutamine repeat (148 glutamines), was not able to induce a phenotype and even did not aggregate. Only nuclear ataxin-3 gave rise to a phenotype. Purely cytoplasmic ataxin-3, however, even with a highly expanded polyglutamine repeat, remained harmless. In addition, we identified and characterized intracellular transport signals (two nuclear export signals, NES, and one nuclear localization signal, NLS) within the coding sequence of ataxin-3. Therefore, it is evident that proteins involved in the nucleocytoplasmic transport machinery recognize these localization signals, control the intracellular localization of ataxin-3, thereby influence the toxicity and aggregation of Ataxin-3 and, thus, the pathogenesis of MJD/SCA3.

We further dissected the nucleocytoplasmic transport mechanisms of ataxin-3 and identified a transport protein whose critical importance for the nuclear import of ataxin-3 we confirmed in vitro and in vivo: Knocking down this protein alleviates the symptoms induced by expanded ataxin-3 both in transgenic Drosophila and mouse models. As pathologically ataxin-3 remains harmless as long as it is kept in the cytoplasm, we further anticipated the intracellular localization of ataxin-3 as a target for a possible therapeutical intervention. For this reason, we generated an assay allowing us to easily monitor the intracellular localization of normal or expanded ataxin-3, screened a library of FDA-approved compounds and indeed identified compounds impacting the nuclear translocation of ataxin-3 and validated them in vivo. As the compounds we identified are already FDA-approved and on the market, they could be transferred to the clinics comparatively fast. We believe that our results will improve the understanding of pathological mechanisms influencing the progression of the disease and are an important contribution towards a treatment of SCA3.

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