



Translation control of mRNAs with CAG repeat expansions and its implication for pathogenesis and therapy of SCA2 and other spinocerebellar ataxias.

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Scientific summary

It has been found that mRNAs with expanded CAG repeat stretches bind to a ribo-nucleo-protein (mRNP) complex that potentiates the protein production from these mRNAs thereby possibly critically contributing to the pathogenesis of CAG repeat expansion disorders including spinocerebellar ataxias. At the core of this complex are the ubiquitin ligase MID1, protein phosphatase 2A (PP2A) and the PP2A subunit $\alpha 4$, which connects the MID1 / PP2A mRNP complex with the translation regulatory mTOR pathway. Drugs like the mood stabilizer lithium, the type II diabetes medication metformin, rapamycin and acetyl salicylate interfere with the PP2A/mTOR/MID1 signalling triage, thereby reducing the production of disease-causing protein from mRNAs with expanded CAG repeats. Using SCA2 as an example in the proposed research programme, this research will elucidate whether the MID1 / PP2A mRNP complex and related RNA gain-of-function mechanisms contribute substantially to the development of spinocerebellar ataxias in tissue culture models, cells from SCA2 patients and an SCA2 mouse model. By using the mentioned drugs, the effectiveness of interfering with the activity of this novel mRNP complex as a novel therapeutic avenue for spinocerebellar ataxias will be determined, with the goal of providing the first available mechanistically-based intervention for these fatal disorders.

Lay summary

Spinocerebellar ataxias (SCAs) are severely debilitating for affected individuals and their families, and impose major costs to society and the healthcare system, because they cause progressive loss of essential physical and mental abilities. They are inherited in an autosomal dominant manner, meaning there is a 50% risk of the condition occurring in children of affected patients. Currently no treatment is available.

We have identified a cluster of molecules which may be critically involved in the development of these disorders. This cluster seems to support the production of disease-causing proteins in patients with SCAs. Using SCA2 as an example, in the proposed research programme we will determine the exact role of the cluster in the development of these neurodegenerative disorders. In addition, certain widely-prescribed existing drugs, including the psychiatric agent lithium and the diabetes drug metformin, appear to act by biochemical actions linked to this newly-discovered molecular cluster. Therefore, we will test the feasibility of using these drugs to develop novel therapeutic strategies for spinocerebellar ataxias to improve patient outcomes, and perhaps even to cure these serious disorders.



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