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MID1: A translational regulator of mRNAs with expanded CAG repeats

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Polyglutamine diseases are monogenic diseases that are caused by elongation of CAG repeat motifs translating into elongated polyglutamine (polyQ) stretches on the protein level. Aggregation of polyQ proteins in the central nervous system of patients is a hallmark of polyQ diseases. Based on the neurotoxic function of these proteins produced from expanded CAG repeats, a reduction of these proteins will be beneficial in the disease context. In line, reduction of polyglutamine protein in disease models for polyglutamine diseases improved the disease phenotype. But how is the protein synthesis rate from expanded CAG repeat mRNAs regulated?

One mechanism that we have recently identified to play a role in regulating the translation of huntingtin (HTT) mRNA with expanded CAG repeats involves the MID1-PP2A complex. Mutant HTT mRNA binds to a protein complex containing the MID1 protein, the catalytic subunit of protein phosphatase 2A (PP2Ac), and 40S ribosomal S6 kinase (S6K) in a CAG repeat length-dependent manner. Strikingly, binding of the MID1 protein complex to mutant HTT mRNA, results in an increased translation and subsequent aggregation of mutant HTT. Interestingly, this sequestration of MID1 to expanded CAG repeats does not seem to be limited to mutant HTT mRNA, but is also seen on other mRNAs with expanded CAG repeats such as mutant ATXN3. This makes the MID1-RNA-protein complex a very interesting target to prevent formation of pathological accumulations of mutant polyQ protein in polyQ disorders.

Biography

Sybille Krauss studied Biotechnology at the Technische Fachhochschule Berlin until 2002. As a graduate student, she worked at the Max Planck Institute for Molecular Genetics and received her PhD in 2005. After this, she conducted research as Post-doc at the Charité in Berlin in the group of Prof. Susann Schweiger. Since 2010 she is group leader at Deutsches Zentrum für Neurodegenerative Erkrankungen in Bonn.

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