Dynamics of ataxin-1 in spinocerebellar ataxia type 1
Krol, H.A.G.

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Chapter 1
General introduction
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Spinocerebellar ataxias

The spinocerebellar ataxias (SCAs) are diseases characterized by progressive neurodegeneration of the cerebellum. The clinical symptoms reflect cerebellar dysfunction, such as problems with the coordination of gait and movements of hands and eyes. Typically, a person with SCA remains cognitively intact, but progressively loose control over muscle movements (Soong and Paulson, 2006). To date, the SCAs are a group of 30 neurodegenerative disorders, that are caused by different types of autosomal dominant mutations in various genes such as coding polyglutamine (CAG) (polyQ) repeat expansions, non-coding (CTG, CAG) repeat expansions or missense or deletion mutations in the coding regions of SCA genes (Duenas et al., 2006). These mutations lead to dysfunction and degeneration of mainly the Purkinje cells in the cerebellum, although other brain areas can also be affected which may contribute to differences between the various SCA types.

The SCA genes play a role in a broad range of cellular processes. Recent studies that focused on the physiologic (wildtype) and pathogenic (mutant) functions of these genes led to the identification of some shared pathways underlying ataxia, such as dysfunctions in gene transcription, synaptic transmission and intracellular signaling pathways such as calcium or glutamate signaling (Carlson et al., 2008; Lim et al., 2006; Seeley et al., 2009). The first question addressed in this thesis is how mutations in different proteins lead to a similar disease phenotype. The common neuropathological and clinical characteristics imply that the biological pathways underlying SCAs are interconnected. Interactions have been found between some of the ataxia proteins (Lim et al., 2006), which strengthens the hypothesis that shared pathways underly ataxia. Understanding of these pathways will allow better understanding of the different mutated proteins that cause similar diseases. This will not only contribute to the understanding of SCAs and neurodegenerative disease in general but will also pave the way to the design of new effective therapies for SCAs. Currently, such therapies are not available.

This thesis focuses on ataxin-1 which is the protein mutated in SCA1, a relatively rare disorder with a prevalence of approximately 1-2 in 100,000 (Mittal et al., 2005). The disease becomes manifest around the 4th decade of life causing death within 15 years. The clinical symptoms of SCA1 vary depending on the length of the polyQ repeat and the stage of the disease. Besides ataxia, these symptoms include dysarthria and swallowing and breathing problems. SCA1 is caused by a CAG repeat expansion mutation in the SCA1 gene, resulting in an ataxin-1 protein with an extended polyQ stretch. This mutation is dominantly inherited and was first discovered in 1993 (Banfi et al., 1994; Chung et al., 1993; Orr et al., 1993; Quan et al., 1995; Ranum et al., 1994).

Therefore, the second question of this thesis is how does polyQ expansion in ataxin-1 induce SCA1? The third question is whether ataxin-1 accumulations present in SCA1 represent polyQ aggregates? It has been shown that the nuclear localization, and not the formation of nuclear inclusions is crucial for the pathogenesis (Cummings et al., 1999; Emamian et al., 2003; Klement et al., 1998). We show that both wildtype and
polyQ-expanded ataxin-1 form multiple nuclear inclusions in vitro, which are dynamic. The observed inclusions do not represent irreversible sequestered aggregates, but represent functional protein complexes with ataxin-1 as one of the components. Therefore, these inclusions should be redefined as nuclear bodies (Chapter 2; Krol et al., 2008).

The aim of this thesis is to unravel the effect of the polyQ expansion on the intracellular function of ataxin-1 and how this can lead to SCA1. Furthermore, we investigate whether there are common pathways for SCAs by studying interactions between SCA1 and SCA14. To address these questions, we applied advanced microscopy on cell models, and biochemistry and histology on mouse SCA1 material.

Outline of the thesis

In chapter 2 of this thesis, we study the dynamics of ataxin-1 nuclear bodies in living cells and show that these structures are fundamentally different from polyQ aggregates. Subsequently, we investigate in chapter 3 whether these nuclear bodies are also present in vivo, using a SCA1 mouse model. Furthermore, we investigated whether the localization and dynamics of three allegedly ataxin-1 interacting proteins, LANP, PQBP-1 and RBM17, are altered when they are co-expressed with mutant ataxin-1. In chapter 4, we search for a common pathway of ataxin-1 and PKCγ (the protein mutated in SCA14) by studying interactions between the two proteins. We also study the effects of PKCγ on ataxin-1 nuclear body formation and dynamics, and vice versa the effects of mutant ataxin-1 on the distribution of PKCγ in SCA1 mouse. In chapter 5, we discuss the different molecular and cellular levels at which mutant ataxin-1 can initiate toxicity. Here, we start in the nucleus and travel towards the cell periphery to discuss normal and toxic functions of ataxin-1 in each cellular compartment.

PolyQ proteins are being degraded by proteases like the proteasome. In the last part of this thesis, chapter 6, we mimic generation of polyQ fragments by the proteasome and examine whether these fragments are degradation-resistant and sufficient to initiate aggregation.

References


