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Kaleidoscopic protein–protein interactions in the life and death of ataxin-1: new strategies against protein aggregation☆

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Understanding how proteins protect themselves from aberrant aggregation is of primary interest for understanding basic biology, protein biochemistry, and human disease. We discuss the paradigmatic example of ataxin-1 (Atx1), the protein responsible for neurodegenerative spinocerebellar ataxia type 1 (SCA1). This disease is part of the increasing family of pathologies caused by protein aggregation and misfolding. We discuss the importance of protein–protein interactions not only in the nonpathological function of Atx1 but also in protecting the protein from aggregation and misfolding. The lessons learned from Atx1 may lead to a more general understanding of the cell's protective strategies against aggregation. The obtained knowledge may suggest a new perspective for designing specific therapeutic strategies for the cure of misfolding diseases.

Cellular mechanisms of protection from protein aggregation

The increasing realization that protein aggregation plays a predominant role in the development of a number of diseases parallels an increasing interest in the mechanisms that protect proteins from this often unwanted phenomenon. Although much has been said about these protection mechanisms, and several possible strategies that the cell may take in combating protein aggregation have been suggested [1–4], our knowledge of the topic remains limited. One of the most interesting hypotheses is that interactions with other cellular partners could have a leading role in preventing protein aggregation [3,5]. Several examples seem to support this hypothesis. It has, for instance, been observed that binding to ligands, including nucleic acids, prevents misfolding of the oncogene p53 [4]. Similarly, the protein ataxin-3 has been found to be protected from aggregation when interacting with the natural cellular partner ubiquitin [6]. These examples in turn suggest that normal function and aberrant aggregation are competing pathways [7].

In this review, we discuss the paradigmatic example of Atx1. This protein provides a unique illustration of how protein–protein interactions can sort the 'fate' of a protein. Atx1 is responsible for SCA1 (OMIM #164400)

Glossary

Ataxia: the word comes from the Greek language and refers to a neurological loss of voluntary coordination of muscular movement. Ataxia is a nonspecific clinical manifestation that implies dysfunction of different parts of the nervous system that coordinate movement, such as the cerebellum. Ataxias can affect anyone of any age and can be both recessive or dominant.
Linear motifs: are short, conserved motifs involved in recognition and targeting functions. These motifs are linear, in that they do not involve 3D organization with sequence-wise distant segments of the molecule. Examples are phosphorylation motifs and NLSs.
Misfolding diseases: a group of diseases caused by protein aggregation and misfolding. Examples are Alzheimer's and Parkinson's diseases.
Oligonucleotide-binding (OB) fold: is a compact structural motif frequently found in proteins involved in nucleic acid recognition. Structural comparison of all OB fold/nucleic acid complexes solved to date confirms the low degree of sequence similarity among members of this family while highlighting several structural determinants common to most of these OB folds.
Polyglutamine diseases: are a family of neurodegenerative diseases caused by the anomalous expansion of a CAG triplet repeat in a specific gene. This leads to an expanded tract of glutamines in the corresponding gene products, which makes the carrier proteins highly fibrillogenic. These diseases include Huntington disease, spinobulbar muscular atrophy, dentatorubral-pallidoluysian atrophy, and several spinocerebellar ataxias.
Protein chameleon: proteins or protein regions that can adopt multiple local or global folds usually because of different environments or sequence variations. This possibility is thought to facilitate evolutionary transitions in protein structure and function. It is rather unusual to observe different conformations (asymmetric subunits) in crystal structures.
Protomer: the term used in structural biology to refer to the smallest subunit that assembles in a defined stoichiometry to form an oligomer. It is, for instance, the monomeric subunit in a dimer.
Spinocerebellar ataxias (SCAs): are progressive neurodegenerative diseases with multiple types, each of which could be considered a disease in its own right.
Structural domains: are a conserved part of a given protein sequence that can evolve, function, and exist independently of the rest of the protein chain. Each domain forms a compact 3D structure and often can be independently stable and folded.
U2AF (U2 auxiliary factor) homology motif (UHM): is an RNA recognition domain that binds to tryptophan-containing linear peptide motifs (ULMs) in several nuclear proteins.
UHM ligand motif (ULM): is a short induced fit linear motif that mediates dynamic interactions between splicing factors.

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[8] (for a definition of ataxia, see the Glossary). SCA1 is a late onset autosomal dominant neurodegenerative disorder characterized by cerebellar ataxia and associated with varying degrees of oculomotor abnormalities, pyramidal and extrapyramidal features, peripheral neuropathy, and cognitive impairment [9]. Until a link with disease was established, Atx1 had largely been overlooked. However, over the last decade or so, a substantial amount of research into the structure and function of Atx1 has started to provide a clearer picture of the cellular role of this protein [10,11].

In the following sections, we review our current knowledge of Atx1 and place these observations within the context of the protection mechanisms against aggregation. We show how the normal function of the protein, together with its unusual structural properties, determine its cellular function/dysfunction and how aggregation is mediated by multiple regions acting in cooperation. We believe that this example may open a new perspective for the study of SCA1 and other misfolding diseases and eventually suggest a strategy for a specific cure.

Atx1 is a member of the polyglutamine expansion diseases

Atx1 is, together with the above mentioned ataxin-3, a member of the family of proteins that contain a polyglutamine (polyQ) tract and are implicated in genetic neurodegenerative diseases [12] (Figure 1A). These pathologies are caused by the anomalous expansion of a polymorphic tract of polyQ, which, when above a threshold of approximately 37 repeats, causes aggregation that is ultimately associated with cell toxicity and neuronal death [12] (Figure 1B). Although rare and diversified in symptoms, these diseases are dominant and currently incurable. Several lines of evidence suggest that polyQ expansion is the necessary event for disease development: attachment of a polyQ stretch to an otherwise healthy protein is sufficient to cause toxicity; interruption of the polyQ tract by even one non-glutamine amino acid appreciably slows down disease and the age at disease onset correlates inversely with the number of uninterrupted polyQ repeats [13]. It has however been recognized that, in addition to polyQ, other regions significantly contribute to the aggregation process. An increasing interest

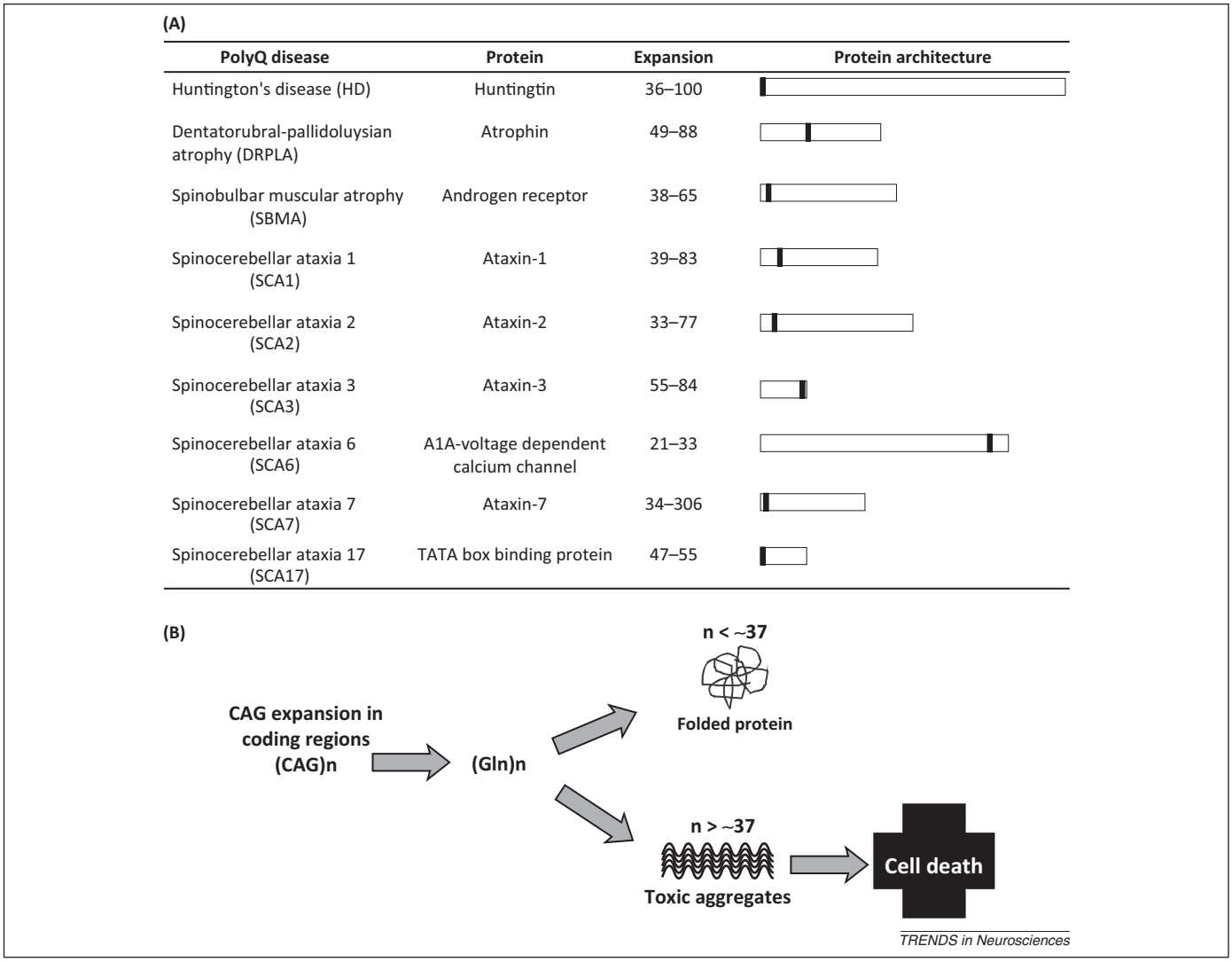

Figure 1. Expansion of a polyglutamine (polyQ) tract in specific proteins is associated with neurodegeneration. **(A)** A list of the currently known polyQ diseases with protein name, pathological threshold, and protein architecture. The position of polyQ in the sequence is indicated as a black rectangle on the protein schematic representation. **(B)** Schematic representation of the disease mechanism. When the repeat number is lower than a threshold (~37 repeats), the proteins are correctly folded and functional; when it is above the threshold, the carrier proteins aggregate and misfold with consequent cell toxicity and death.