Analysis of Ataxin-2 and other Lsm domain proteins

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Abstract

Sm and Sm-like proteins of the RNA-binding Lsm (Like Sm) domain family are generally involved in important processes of RNA metabolism including RNA modification, splicing, and degradation [1]. Lsm proteins can occur in large complexes and form cyclic hetero- or homo-oligomers [2]. While recent research has focused on the function and structure of small Sm and Sm-like protein (not more than about 150 residues), little is known about Lsm domain proteins with additional domains and sequence motifs.

Two very long Lsm domain proteins with both N- and C-terminal sequence extensions are the human ataxin-2 (1312 residues) of unknown cellular function and its yeast homolog PBP1 (PAB1-binding protein 1) [3,4]. A polyglutamine expansion in the N-terminal region of ataxin-2 is causative of the inherited neurodegenerative disorder spinocerebellar ataxia type 2 (SCA2) [5]. This disorder belongs to a heterogeneous group of trinucleotide repeat disorders including Huntington's disease and several other spinocerebellar ataxia types such as SCA1, SCA3, and SCA7 [6].

The C-terminal regions of the homologs ataxin-2 and PBP1 contain binding sites for A2BP (ataxin-2 binding protein) of unknown function or PABP (poly(A)-binding protein) [7,8], respectively. Both A2BP and PABP possess N-terminal RNA recognition motifs (RRMs) and may be evolutionarily and functionally related. The C-terminal tail of PBP1 has been observed in experiment to bind the C-terminal PABC domain of PABP and to regulate polyadenylation in mRNA splicing [4]. The absence of PBP1 leads to incomplete poly(A) tails, although the 3'-end of pre-mRNA is properly cleaved.

In order to obtain functional hypotheses on ataxin-2, we performed a comprehensive bioinformatics analysis on the structure and function of ataxin-2 and on the yeast interaction network of PBP1. Further experiments including a yeast-2-hybrid screen with ataxin-2 support our predictions of an important role of ataxin-2 in RNA metabolism. We also found at least five novel and evolutionarily conserved Lsm domain proteins with as yet uncharacterized C-terminal tails. Based on yeast interaction data, we could assign putative functions such as RNA methylation and mRNA degradation to some of the new Lsm domain proteins.

Our project web site provides further information: http://www.mpi-sb.mpg.de/~mario/medbioinf/

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