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ABSTRACT BOOK

FRAMESHIFT MUTATIONS IN THE HEAT SHOCK PROTEIN B8 CAUSE ITS AGGREGATION AND IMPAIR PROTEOSTASIS IN NEUROMYOPATHIES

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The heat shock protein B8 (HSPB8) is a chaperone highly expressed in muscle cells, where it favors the chaperone-assisted selective autophagy (CASA) of damaged structural proteins. In neurons, HSPB8 enhances the clearance of misfolded proteins associated with motoneuron diseases. This is achieved by the interaction of HSPB8 with the cochaperone BAG3, forming the CASA complex together with the heat shock protein family A (HSPA) and the E3-ubiquitin ligase STUB1. The chaperones of the CASA complex recognize the substrate, which might undergo refolding or STUB1-mediated ubiquitination. Therefore, ubiquitinated proteins can be targeted to autophagic degradation. Different frameshift mutations in the *HSPB8* gene have been identified in neuromyopathies. These *HSPB8* frameshift mutations cause the elongation of the HSPB8 protein product at the carboxy-terminus and a variable modification of the carboxy-terminal domain. Here, we show that the HSPB8 frameshift mutants are characterized by high insolubility and aggregation propensity. The HSPB8 frameshift mutants retain the ability to take part in the CASA complex, determining the sequestration of the HSPB8 wild-type and the other components of the CASA complex. As a result, misfolded and ubiquitinated substrates are entrapped in HSPB8-mutants aggregates together with autophagy receptors. Notably, we show that HSPB8 mutant aggregation is driven by neither the other CASA members nor autophagy receptors. Instead, we found that the mutated carboxy-terminal sequence of the HSPB8 mutants possesses intrinsic properties to aggregation. In summary, here we describe a gain of toxic function mechanism through which different HSPB8 frameshift mutations may cause neuromuscular diseases.