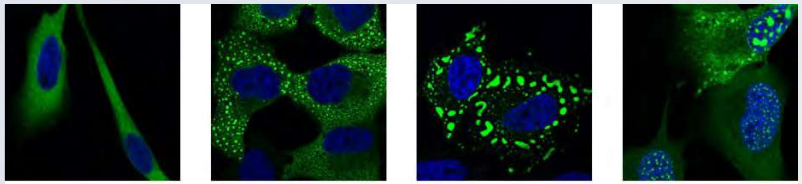
The 4th Cell Stress Society International workshop on

Small Heat Shock Proteins



The beauty and the complexity of the Small Heat Shock Proteins

Program

17-18 November 2022

4th CSSI workshop on Small Heat Shock Proteins

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Abstract Title:
Frameshift mutations in the Heat Shock Protein B8 share common pathogenic mechanisms and impair proteostasis

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Abstract:
The Heat Shock Protein B8 (HSPB8) is highly expressed in muscles where it favours the Chaperone Assisted Selective Autophagy (CASA) of damages structural proteins. In neurons, HSPB8 enhances the clearance of misfolded substrates, such as those associated with motoneuron diseases. This is achieved by the interaction of HSPB8 with the co-chaperone BAG3, forming the CASA complex together with the HSP70 and the E3-ubiquitin ligase CHIP. When misfolded proteins are recognized by the chaperones of the CASA complex, they can be refolded or routed to aggresomes for autophagy-mediated degradation. Frameshift mutations in *HSPB8* gene have been reported in neuromuscular diseases. 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 expression of the HSPB8 frameshift mutants associates with insolubility and aggregation propensity. The HSPB8 frameshift mutants retain the ability to take part in the CASA complex, determining the sequestration of the HSPB8 wildtype, BAG3, HSP70 and CHIP. As a result, misfolded and ubiquitinated substrates are entrapped in HSPB8-mutants aggregates together with autophagy receptors and CASA members. Notably, HSPB8 mutants aggregation is not driven by the CASA members, although BAG3 depletion affect aggregate number and size. Autophagy receptors do not cause HSPB8 mutants aggregation as well. Instead, we found that the elongated carboxy-terminus of 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.