Tuning the Stress Response Pathway to respond to mHTT Aggregation

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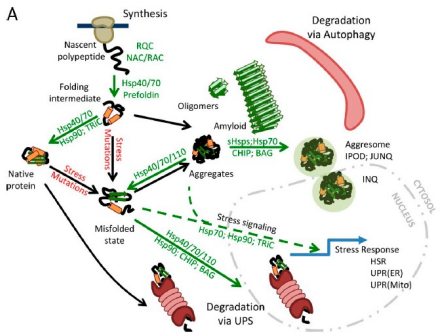
Summary

Here we describe the identification of factors that enable cells to efficiently sense and respond to pathogenic protein aggregates, such as mutant Huntingtin, via endogenous cellular stress response pathways.

Introduction

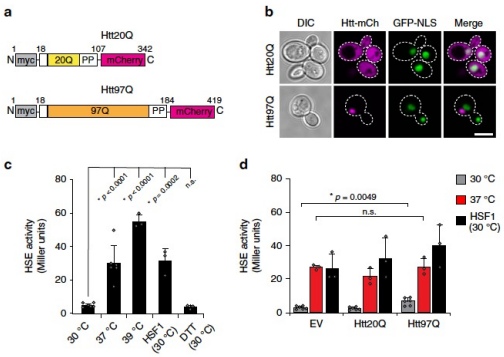
The Cytosolic Stress Response is Adaptive



Cells can recognize and clear misfolded or aberrant protein species, for example, those that arise during heat stress, through the upregulation of protein quality control components via the HSF1-regulated cellular stress response. Unfortunately, this pathway is not activated upon the aggregation of pathogenic proteins like mutant Huntingtin (mHTT). Yet, artificial HSF1 activation can enlargen the cellular capacity to handle mHTT aggregates and reduce toxicity in many model systems.

Klaips CL, Jayaraj GG, Hartl FU, J Cell Biol, 2017

PolyQ Aggregates do not Trigger a Stress Response

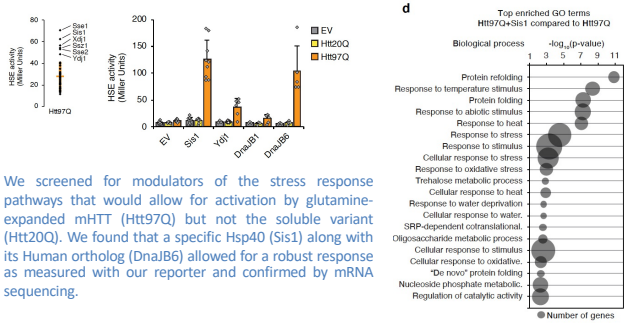


Yeast provide an ideal model system for studying huntingtin aggregation as aggregates form in a glutamine-length dependent manner without overt toxicity. The presence of these aggregates is not sufficient to trigger the endogenous stress response pathways as measured using a heat shock element containing reporter. Yet, the stress response pathways are still functional, as they can be activated by heat treatment.

Klaips CL, Gropp MHM, Hipp MS, Hartl FU, Nat Comm, 2020

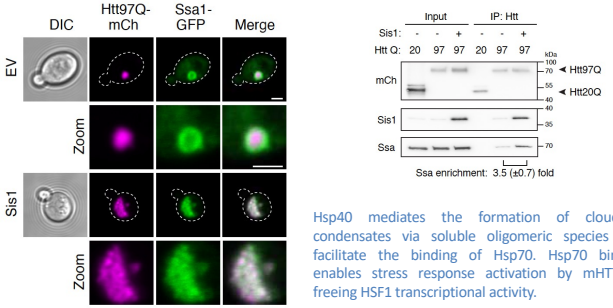
Results

The Stress Response can be modulated by Sis1



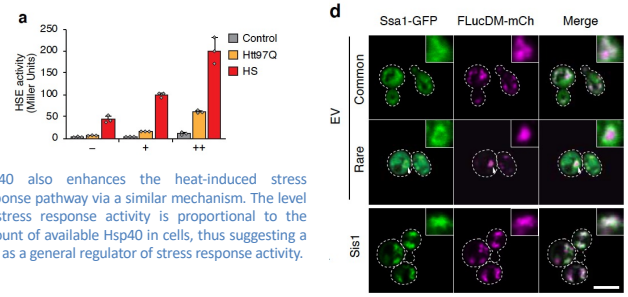
We screened for modulators of the stress response pathways that would allow for activation by glutamine-expanded mHTT (Htt97Q) but not the soluble variant (Htt20Q). We found that a specific Hsp40 (Sis1) along with its Human ortholog (DnaJB6) allowed for a robust response as measured with our reporter and confirmed by mRNA sequencing.

Hsp40 enables the Formation of Cloud-like aggregates that bind to Hsp70



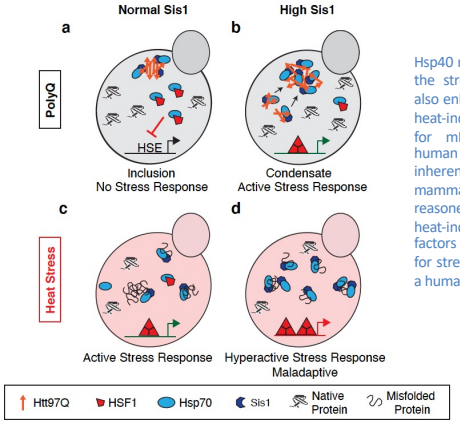
Hsp40 mediates the formation of cloud-like condensates via soluble oligomeric species that facilitate the binding of Hsp70. Hsp70 binding enables stress response activation by mHTT by freeing HSF1 transcriptional activity.

Hsp40 also enhances the heat-induced stress response



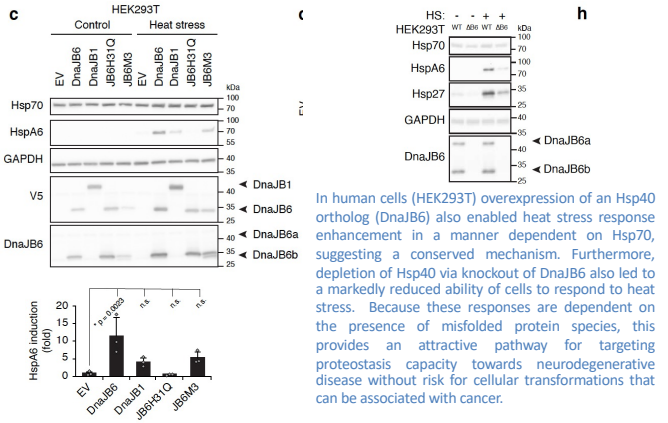
Hsp40 also enhances the heat-induced stress response pathway via a similar mechanism. The level of stress response activity is proportional to the amount of available Hsp40 in cells, thus suggesting a role as a general regulator of stress response activity.

Hsp40 regulates the Stress Response in an Aggregate-dependent Manner



Hsp40 not only enables activation of the stress response by mHTT, but also enhances the stress response to heat-induced aggregates. Screening for mHTT-based activators in a human system is difficult due to inherent toxicity of the aggregates in mammalian cellular models. We reasoned that we could utilize the heat-induced effect to screen for factors that could potentially allow for stress response activation also in a human-cell based model.

Sis1 Mediates the Toxicity of PolyQΔP



In human cells (HEK293T) overexpression of an Hsp40 ortholog (DnaJB6) also enabled heat stress response enhancement in a manner dependent on Hsp70, suggesting a conserved mechanism. Furthermore, depletion of Hsp40 via knockout of DnaJB6 also led to a markedly reduced ability of cells to respond to heat stress. Because these responses are dependent on the presence of misfolded protein species, this provides an attractive pathway for targeting proteostasis capacity towards neurodegenerative disease without risk for cellular transformations that can be associated with cancer.

Conclusion

We have identified positive modulators of the stress response that work in an aggregate-specific manner. This novel pathway utilizes the cell's own stress-sensing mechanisms to combat toxic mHTT effects, and does not affect wild type Huntingtin. It is also expected to work synergistically with current RNAi-based approaches to decrease mHTT protein levels.