Heat shock factor 1 is a direct anti-amyloid factor: connecting neurodegeneration and uncontrolled growth

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Worldwide, more than 40 million people are afflicted with Alzheimer's disease (AD) (Esquerda-Canals et al., 2017). AD is a devastating neurodegenerative disroder characterized by progressive decline in cognitive abilities. A hallmark of AD and other neurodegenerative disorders in humans is the aggregation of proteins into amyloid fibrils and their deposition into plaques and intracellular inclusions (Iadanza et al., 2018). In AD, following a series of proteolytic cleavage events amyloid precursor proteins give rise to Aβ monomers, which, in turn, assemble into soluble amyloid oligomers (AOs) that ultimately become insoluble mature amyloid fibrils enriched with highly ordered cross β-sheet structures. This entire process is termed as amyloidogenesis (Chen et al., 2017).

Heat shock factor 1 is a potent anti-amyloid factor: In mammals, heat shock factor 1 (HSF1) is the master regulator of the heat-shock response (HSR), an evolutionarily conserved cytoprotective transcriptional program defined by a marked induction of heat-shock proteins (HSPs) in the face of environmental stressors (Morimoto, 2011). HSPs are molecular chaperones that play a key role in preserving proteomic stability, by ensuring the proper folding of other proteins, promoting the ubiquitination and proteasomal degredation of misfolded/damaged proteins, as well as facilitating the assembly of multiprotein complexes (Dai and Sampson, 2016). HSF1 and its mediated HSR, unsurpisingly, have been closely implicated in a variety of neurodegenerative disorders (Gomez-Pastor et al., 2018). In particular, HSF1 expression is diminished in AD patients and relevant mouse models; conversely, overexpression of a constitutively active HSF1 mutant rescues the cognitive defects in a rat AD model (Jiang et al., 2013). Nonetheless, the underlying mechanism of action of HSF1 has been exclusively ascribed to its canonical transcriptional regulation of the HSR. Unexpectedly, a new study uncovered that HSF1 is capable of impeding amyloidogenesis via physical interactions (Tang et al., 2020), an exciting finding supported by three independen lines of evidence. First, *in vitro* thioflavin T binding assays evidently indicated that recombinant HSF1 proteins blocked $A\beta_{1-42}$ fibrillation in a dose-dependent manner (**Figure 1A**). Second, this blockade of amyloid fibrillation was also visualized by transmission electron microscopy. While incubated with GST, $A\beta_{1-42}$ assembled into mature fibrils spontaenously, as expected; by contrast, incubation with HSF1 at a 1:4 molar ratio eliminated amyloid fibrils but resulted in amorphous aggregates instead (**Figure 1B**). Third, the impeded amyloidogenesis by HSF1 was further confirmed by marked reductions in AOs and amyloid fibrils, quantitated by the widely used conformation-specific A11 and OC antibodies (Tang et al., 2020).

Mechanistically, this new study suggested that HSF1 physically neutralizes soluble AOs, both A11- and OC-immunoreactive, to block amyloidogenesis. Accumulating evidence has already pinpointed soluble AOs as a prime neurotoxic amyloid species in human neurodegenerative disorders. Revealed by this study, soluble AOs directly attack the essential mitochondrial chaperone HSP60, prompting its polyubiquitination, proteasomal degradation and aggregation. Consequently, the mitochondrial proteomic instability instigates, inevitably triggering apoptosis and mitophagy. Through physical neutralization of AOs, HSF1 shields HSP60 against the assaults, thereby averting the mitochondrial damage and cytotoxicity. Despite being uncovered in mouse models, these mechanisms are validated in both primary human neuron cultures and brain specimens of AD patients (Tang et al., 2020).

Implications in AD, overgrowth syndromes and cancer: Apart from revealing previously unrecognized molecular mechanisms, this new study may bear important implications for understanding human AD and beyond, including overgrowth syndromes and cancer. First, amyloidogenesis alone appears insufficient to provoke cellular toxicity. HSF1, as a pivotal line of defense, dictates whether amyloids exert toxic effects or not. It has long been observed in human AD that amyloid loads are poorly correlated with neurotoxicity and clinical symptoms, a major criticism of "the Amyloid Hypothesis" (Selkoe and Hardy, 2016). Thus, this finding may offer an explanation for this hotly debated issue. Second, this study reveals that the AO:HSF1 molar ratio determines cytotoxicity.

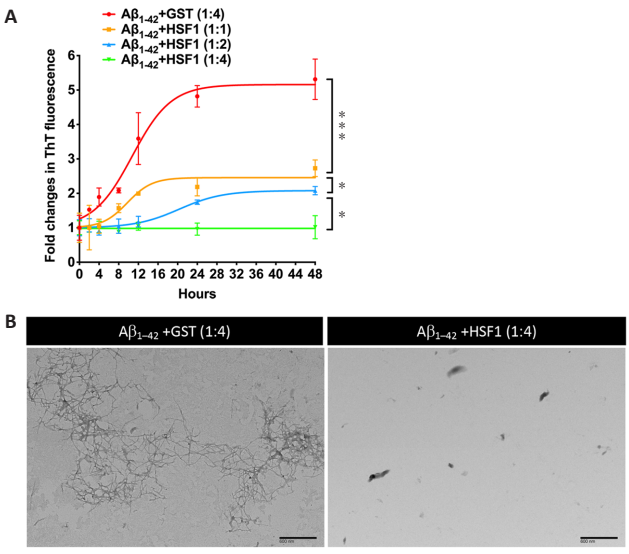

Figure 1 | **HSF1 blocks *in vitro* $A\beta_{1-42}$ amyloidogenesis.**
(A) Quantitation of the fibrillation of $A\beta_{1-42}$ incubated with recombinant HSF1 proteins *in vitro* at increased molar ratios by the ThT binding assay. Recombinant GST served as the control. The curves are fitted with the Boltzmann sigmoid equation (*$P < 0.05$, ***$P < 0.001$). (B) Visualization of *in vitro* fibrillation of $A\beta_{1-42}$ coincubated with either GST or HSF1 (1:4 molar ratio) at 37°C for 48 hours by transmission electron microscopy. Scale bars: 600 nm. Unpublished data. Aβ: Amyloid beta; GST: glutathione-S-transferase; HSF1: heat shock factor 1; ThT: thioflavin T.

The AO-HSP60 interaction signifies the breach of HSF1 defense, which may be exploited to predict the clinical progression of human AD. Third, HSF1 is able to both disrupt the existing AO-HSP60 interactions in human AD brain lysates and markedly suppress Aβ-induced toxicity in cultured human neurons. These findings collectively suggest a therapeutic potential of HSF1 in combating AD and other neurodegenerative disorders. Fourth, whereas the vast majority of AD in humans are sporadic, their underlying causes still remain largely elusive, in sharp contrast to familial AD. A notable finding of this new study is that uncontrolled protein synthesis is causally related to amyloidogenesis. Intriugingly, heightened AKT/mTORC1 signaling, a potent stimulator of protein translation, has been detected in human AD brains (Griffin et al., 2005). Thus, dysregulated protein translation in neurons during aging may contribute to the emergence of amyloids in sporadic human AD, a plausible postulation warranted for further investigations. Fifth, this study reveals that amyloidogenesis is also associated with tissue/organ overgrowth, beyond AD. This previously unknown phenomenon suggests that amyloidogenesis may be an inevitable consequence of uncontrolled growth, a condition occurring in human cancer as well. In line with this, amyloidogenesis has been detetected in cancerous cells; importantly, HSF1 suppresses amyloidogeneis, thereby promoting oncognesis (Tang et al., 2015). Conceptually, these studies suggest that amyloidogenesis may be a checkpoint mechanism to constrain uncontrolled growth and safeguard tissue homeostasis, providing insights into its newly emerged tumor-suppressive role (Tang et al., 2015). Moreover, the anti-amyloid effect of HSF1 corroborates the broadly recognized "HSF1 addiction of cancer" (Dai and Sampson, 2016).

Conclusions and future directions: In summary, this new study provokes fresh thinking about overgrowth, cancer and neurodegeneration. These three distinct human pathologies all converge upon proteomic instability and, in particular, amyloidogenesis. While the anti-amyloid effect of HSF1 bestows neuroprotection, it enables overgrowth and malignancy. Thus, HSF1 may balance the two prominent age-related human diseases, cancer and neurodegenerative disorders, which, intriguingly, display inversely correlated incidences (Plun-Favreau et al., 2010).

Despite these initial findings, several outstanding questions remain. For instance, can HSF1 antagonize amyloids other than Aβ? In another word, is HSF1 a generic anti-amyloid factor? Moreover, how does HSF1 exert its potent anti-amyloid effect? Apparently, HSF1 can do so via physical interactions; nonetheless, the interaction interfaces or amino acid residues on HSF1 that are crucial to this effect still remain to be delineated. Subsequently, can HSF1 mimetics exhibit therapeutic effects in various *in vivo* AD models? Although uncontrolled protein translation contributes to amyloidogenesis, the precise underlying mechanisms are still elusive. Ultimately, can uncontrolled protein translation, particularly owing to hyperactivation of AKT/mTORC1 signaling, in a subset of brain neurons mimic sporadic human AD in mouse models? Elucidation of these questions will help gain insights into the molecular mechanisms underlying amyloidogenesis, advance our understanding of the pathogenesis of sporadic human AD, and pave the way for harnessing this anti-amyloid power of HSF1 to combat AD and cancer.

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