Heat shock factor-1 influences pathological lesion distribution of polyglutamine-induced neurodegeneration

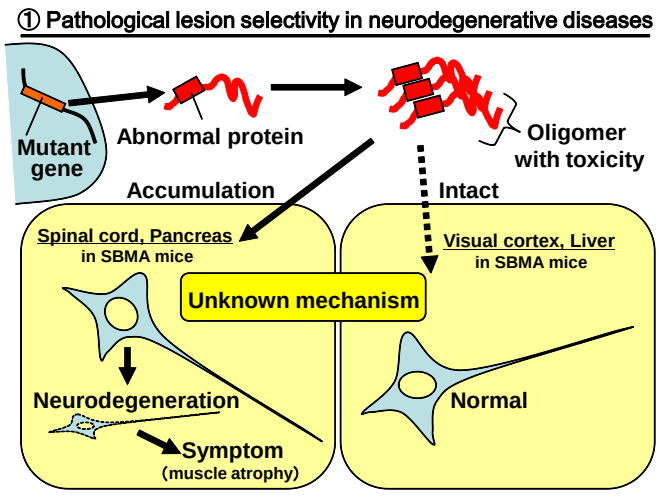
Highlights:

- Heterozygous *Hsf-1* knockout expanded the distribution of pathological lesions in a mouse model of spinal and bulbar muscular atrophy (SBMA), a polyglutamine-induced neurodegenerative disorder.
- Lentiviral-mediated delivery of HSF-1 into the brain of SBMA mice topically suppresses the pathogenic AR accumulation and neuronal atrophy.
- These results suggest that Hsf-1 contributes to the determination of the pathological lesion selectivity in SBMA.

Summary

Naohide Kondo (Visiting fellow), Masahisa Katsuno (Associate professor), and Gen Sobue (Professor) et al., at Nagoya University Graduate school of Medicine (Dean: Masahide Takahashi, MD, PhD) discovered that heat shock factor-1 (Hsf-1) influences the pathological lesion selectivity in spinal and bulbar muscular atrophy (SBMA). This research finding has been reported in Nature Communications on January 29 in 2013.

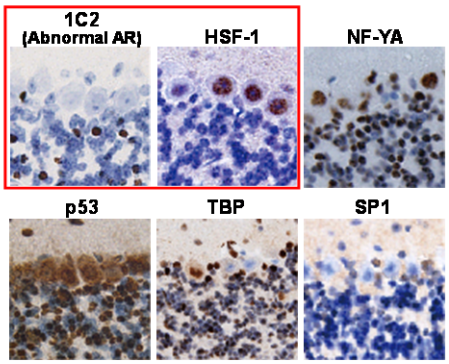
1. Research Background



Late-onset neurodegenerative disorders have an essential feature that abnormal proteins accumulate in specific regions, whereas the disease-causing mutant genes are broadly expressed (Fig.①). Heat shock factor-1 (Hsf-1) induces the expression of Hsps, such as Hsp70, molecular chaperones that play a protective role in the neurodegenerative process by refolding and solubilizing pathogenic proteins. To elucidate the role of Hsf-1 in pathological lesion selectivity of spinal and bulbar muscular atrophy (SBMA), an adult-onset motor neuron disease, here we investigate the effect of Hsf-1 on the pathogenesis of the SBMA mouse model.

2. Research Results

② Hsf-1 levels are associated with pathogenic AR accumulation

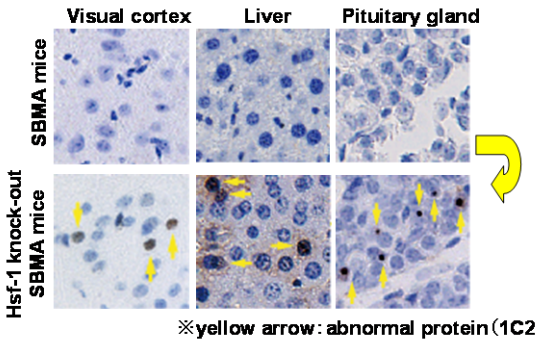


※ Cerebellum of SBMA mouse

※ Hsf-1 expression levels are associated with the accumulation of pathogenic androgen receptor (AR). This relationship was not observed for NF-YA, p53, TBP, or SP1, which are other potential inducers of Hsps.

We performed immunohistochemistry and western blotting of various tissues from wild-type; AR-97Q (SBMA model mouse: 97Q Tg/-, Hsf-1 +/+); and AR-97Q *Hsf-1* +/- (Hsf-1 knockout SBMA mouse: 97Q Tg/-, Hsf-1 +/-) mice using anti-Hsf-1, anti-Hsp70 and anti-polyglutamine (1C2) antibodies. Moreover, we analyzed the effect of lentiviral over-expression of HSF-1 in AR-97Q mice. Our results showed that the expression levels of Hsf-1 are associated with the degree of pathogenic androgen receptor (AR) accumulation in the mice and patients with SBMA. For example, in the cerebellum of AR-97Q mice, there was a scarce accumulation of pathogenic AR in Purkinje cells, where Hsf-1 was expressed at a high level. Conversely, there were abundant 1C2-positive cells in the cerebellar granular cell layer, which showed scarce immunoreactivity for Hsf-1 (Fig.②). In Hsf-1 knockout SBMA mice, abnormal AR accumulates in the cerebral visual cortex, liver, and pituitary, which are not affected in their genetically unmodified counterparts (Fig.③). In the spinal anterior horn and other part of central nervous system of AR-97Q *Hsf-1* +/- mice, the accumulation of mutant AR was substantially enhanced through the down-regulation of Hsp70. Furthermore, the lentiviral over-expression of HSF-1 attenuated the pathogenic AR accumulation in the motor cortex and striatumof AR-97Q mice. In addition, the neuron sizes of the motor cortex and striatum were significantly increased by the HSF-1 injection.

③ Hsf-1 depletion expands distribution of AR accumulation



※yellow arrow：abnormal protein（1C2 staining）

※ In heterozygous *Hsf-1*-knockout SBMA mice, abnormal AR accumulates in the cerebral visual cortex, liver, and pituitary, which are not affected in their genetically unmodified counterparts.

3. Research Summary and Future Perspectives

Our results suggest that Hsf-1 influences the pathological lesion selectivity in SBMA. Since Hsf-1 is known to have diverse functions in healthy and disease conditions such as longevity and inflammation, further study is needed to thoroughly understand the entire effects of *Hsf-1* depletion on the pathogenesis of neurodegenerative diseases including Alzheimer`s disease and Parkinson disease. From the therapeutic point of view, the manipulation of tissue-specific regulatory systems of Hsps may be a key strategy to combat the toxicity of polyglutamine-expanded proteins.

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