Mask, the *Drosophila* Ankyrin repeat and KH domain-containing protein, modulates lifespan and neurodegeneration

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Introduction

- **Processes related to aging and neurodegeneration observed in conditions such as Alzheimer's are associated with the misfolding and aggregation of intracellular proteins.**
- ***Drosophila* is frequently used as a model to study the role of various genes which have human homologues in disease and associated processes.**
- **Mask, a conserved Ankyrin repeat and KH-domain containing protein in *Drosophila*, plays important roles in both mitotically active and post-mitotic cells.**
- **Both ANKHD1 and ANKRD17 are human homologs of *mask,* and mutations in ANKRD17 are associated with adverse conditions such as intellectual disability, while upregulation of ANKHD1 is linked to cancer.**
- **Thus, the loss-of-function mutations of *mask* and its human homologues may result in defective neural functions, while gain-of-function mutations of this gene could promote cell survival and enhanced functions.**
- **In our studies, we aimed to characterize the function of *mask* in *Drosophila* neurons in both synaptic formation and neuro-protective processes.**

Methods

- **Using genetic loss-of-function mutations of *mask* and RNAi knockdown approaches, we examined the roles of *mask* in regulating synaptic formation (data not shown).**
- **In a separate study, we overexpressed Mask in the simple fly eye models for human neurodegenerative diseases where we expressed MAPT, FUS and TD43, well known human proteins whose mutations are associated with the development of Alzheimer's and ALS diseases.**

Figure 1.

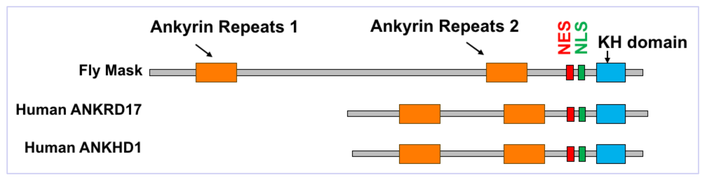

Figure 1. Mask, a *Drosophila* protein, and its human homologs ANKRD17 and ANKHD1. Conservations among the genes are found not only with the overall domain arrangement and structures but also within each functional domains- Nuclear localizing and export signals (NLS and NES), the KH domain and Ankyrin repeats.

Figure 2.

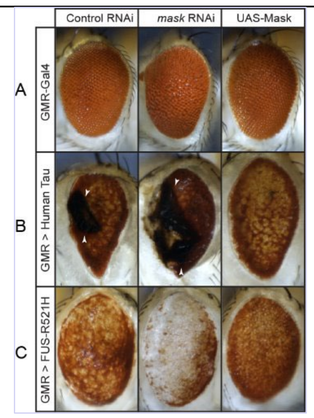

Figure 2. Mask suppresses eye degeneration in *Drosophila* induced by ectopic MAPT and FUS expression. (A) Representative images of adult eyes expressing *UAS-control RNAi, UAS-mask RNAi, and UAS-mask* under the control of GMR-Gal4 driver. (B) Co-expressing these transgenes with human MAPT or (C) with FUS. Note the degeneration in the eyes with MAPT or FUS alone, versus *mask* knockdown, or Mask overexpression. Degeneration from MAPT and FUS is enhanced with *mask* knockdown and suppressed by Mask co-expression.

Figure 3.

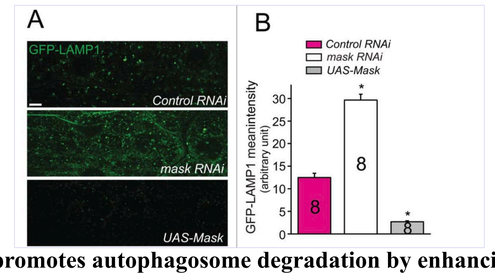

Figure 3. Mask promotes autophagosome degradation by enhancing lysosomal functions. GFP-LAMP1 is used as a marker for lysosomal acidification. The higher GFP signal corelates with higher pH in the lumen of lysosome and thus poor acidification and functions. (A) Representative confocal images of 3rd instar larval muscles expressing GFP-LAMP1 in control, *mask* RNAi, or Mask overexpression animals. (B) quantifications of GFP intensities. Note the increased GFP intensity in the *mask* knockdown muscles versus control and the decreased GFP intensity in Mask overexpression muscles.

Results

- **We demonstrated that loss-of-function mutations in *mask* lead to abnormal synaptic zone morphology and active zone formation (data not shown here).**
- **In contrast to loss-of-function mutations of *mask*, co-expression of Mask with Tau (MAPT), FUS, or TD43 significantly suppressed cell degeneration caused by these proteins in fly eyes.**
- **We showed that Mask elicits these protective effects by promoting autophagy and the clearance of toxic protein aggregates.**
- **We also showed that overexpressing Mask in small groups of dopaminergic neurons can extend the lifespan of flies by up to 50% (data not shown here).**

Conclusion

- **Using *Drosophila* as a model for neurodegeneration in humans, we were able to show the protective role of the Mask protein in neurodegeneration associated with Alzheimer's disease and ALS.**
- **Building on these findings, we will set out to further explore whether the human homolog of *mask,* ANKHD1, may confer similar beneficial effects in mitigating neuronal degeneration in mouse models for the same neurodegenerative conditions.**

References

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