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Article

# A Liquid-to-Solid Phase Transition of the ALS Protein FUS Accelerated by Disease Mutation

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## Highlights

- The ALS-associated protein FUS forms liquid compartments *in vivo* and *in vitro*
- Liquid compartment formation is dependent on the prion-like low-complexity domain
- Liquid compartments of FUS convert with time into an aberrant aggregated state
- ALS patient mutations accelerate aberrant phase transitions of FUS

## Summary

Many proteins contain disordered regions of low-sequence complexity, which cause aging-associated diseases because they are prone to aggregate. Here, we study FUS, a prion-like protein containing intrinsically disordered domains associated with the neurodegenerative disease ALS. We show that, in cells, FUS forms liquid compartments at sites of DNA damage and in the cytoplasm upon stress. We confirm this by reconstituting liquid FUS compartments *in vitro*. Using an *in vitro* “aging” experiment, we demonstrate that liquid droplets of FUS protein convert with time from a liquid to an aggregated state, and this conversion is accelerated by patient-derived mutations. We conclude that the physiological role of FUS requires forming dynamic liquid-like compartments. We propose that liquid-like compartments carry the trade-off between functionality and risk of aggregation and that aberrant phase transitions within liquid-like compartments lie at the heart of ALS and, presumably, other age-related diseases.

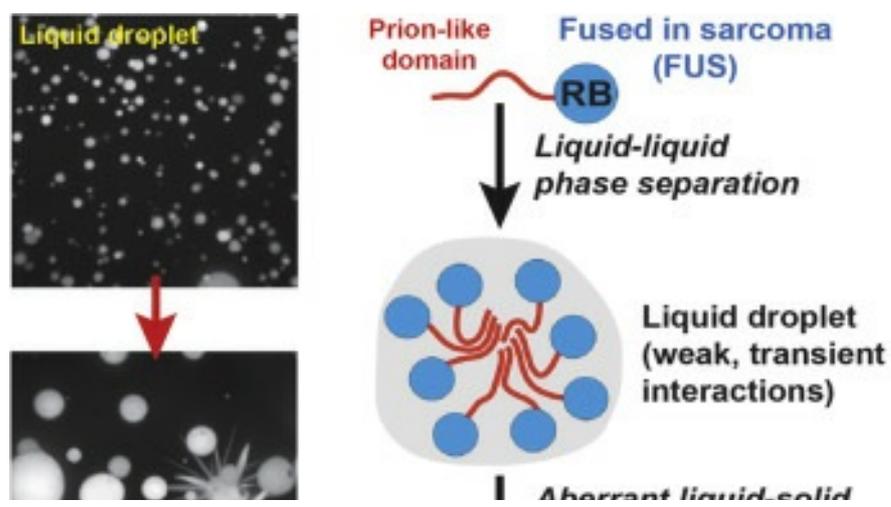
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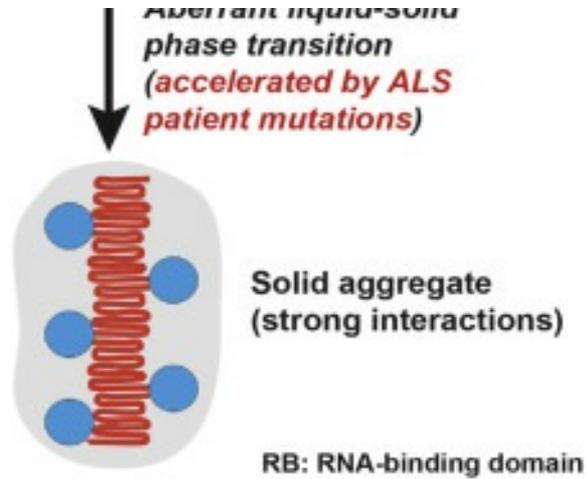
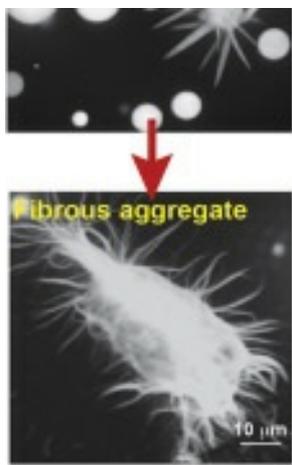


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