RESEARCH HIGHLIGHT

FUSTer than stress granules: a prion-like domain warns plants of heat

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Although plants are poikilothermic organisms with a limited capacity for thermoregulation, they must still sense temperature to survive adverse conditions. Geng and colleagues show that plants possess a thermosensor protein, FUST1, which phase separates through its prion-like domain in response to rising temperatures, forming condensates that prime stress granule assembly and enhance thermotolerance.

As global temperatures rise, heat stress (HS) has become a major threat to plant survival and productivity. Understanding the molecular mechanisms underpinning plants' ability to perceive and respond to elevated temperatures is crucial for developing future climate-resilient crops. A fascinating area of research is the emerging role of biomolecular condensates in plant stress responses.[1] Biomolecular condensates are subcellular droplets or aggregates that form usually through the phase separation of proteins and nucleic acids. Recent research has revealed that these dynamic assemblies, found in the nucleus, cytoplasm, and even on the cell surface, are crucial players in how plants sense temperature shifts.[1–5] Many proteins in condensates are intrinsically disordered proteins (IDPs), rich in low-complexity regions, such as prion-like domains (PrLDs).[6] One type of cytoplasmic biomolecular condensate is stress granules (SGs), which are paramount in plant responses to HS. SGs act as a sorting centre where specific mRNAs are stored for later translation when stress subsides.[1] SG formation is triggered by the inhibition of translation initiation, leading to the accumulation of untranslated mRNAs. These mRNAs, along with RNA-binding proteins (RBPs), are then recruited into SGs. SG composition is dynamic and varies depending on the type and duration of stress. In addition to RBPs, SGs also include molecular chaperones and various enzymes. By sequestering mRNAs and proteins, SGs protect them from degradation and promote cell survival during HS.[1]

A fundamental gap in our knowledge lies in understanding the precise mechanisms that govern condensation of proteins and nucleic acids in response to temperature fluctuations. In a recent study published in *Cell Research*, Geng et al.[7] directly tackle this challenge by delving into a hitherto unknown IDP, FUST1, of the model plant *Arabidopsis thaliana*. The authors demonstrate that FUST1 rapidly forms cytoplasmic condensates upon HS through phase separation, driven primarily by a PrLD at the protein's C-terminus. Using a combination of live-cell imaging, in vitro phase separation assays, and all-atom molecular dynamics, the authors reveal that FUST1 condensation is tightly temperature-sensitive. A "lock-to-open" conformational change within the PrLD promotes multivalent interactions at higher temperatures, enabling FUST1 to condense into dynamic liquid-like granules (Fig. 1a).

Importantly, FUST1 condensation occurs earlier than the assembly of classical SG markers such as G3BP5 and PAB2. This indicates that FUST1 does not simply localize to SGs, but rather primes their formation. Accordingly, loss-of-function *fust1* mutants show significant delays in SG assembly and marked sensitivity to HS, including increased cell death occurrence and impaired seedling recovery after HS. Reintroducing wild-type FUST1, but not the PrLD-deficient FUST1, rescues these phenotypes, highlighting the indispensable role of PrLD-mediated condensation in FUST1 function.

Mechanistically, FUST1 condensation displays lower critical solution temperature behavior: increasing temperature lowers the threshold concentration for droplet formation.[8] In silico molecular simulations reveal that at lower temperatures, a β-strand structure in the PrLD stabilizes an autoinhibited, locked conformation that prevents condensation (the "lock" state). Heat induces a transition to an open state, allowing increased valency and intermolecular contacts to form. In particular, the tyrosine residues are crucial for both phase separation and these heat-dependent conformational rearrangements, but the spacer residues, in particular the hydrophobic ones, also make key contributions. Mutations disrupting the β-strand lock eliminate heat responsiveness of FUST1, in vitro and in planta. Similarly, a recently established and consolidated amino acid sequence grammar drives phase separation of PrLDs in non-plant proteins, with tyrosines playing a key role in condensation.[9] RNA enhances FUST1 condensation, and FUST1 binds RNA nonspecifically through a positively charged patch situated towards the N-terminally located ubiquitin-associated (UBA) domain, linking FUST1 condensation behavior to RNA metabolism during HS (Fig. 1b).

Proteomic analyses, using TurboID proximity labeling and immunoprecipitation-mass spectrometry, identified FUST1's interacting partners as key components of SGs and RNA processing complexes, reinforcing its central role in SG biology. In vitro reconstitution assays further show that FUST1 can partition multiple SG marker proteins into its condensates, even in the absence of stress, suggesting that it acts as a seed for granule nucleation (Fig. 1b). Interestingly, FUST1 condensation also appears to be reversible and dynamically regulated, consistent with the liquid-like nature of SGs. Importantly, FUST1 orthologs from other plant species also exhibit heat-dependent condensation, and their PrLDs retain conserved sequence features critical for the lock-to-open switch. This suggests that FUST1-mediated SG priming is a deeply conserved strategy among land plants for thermoadaptation.

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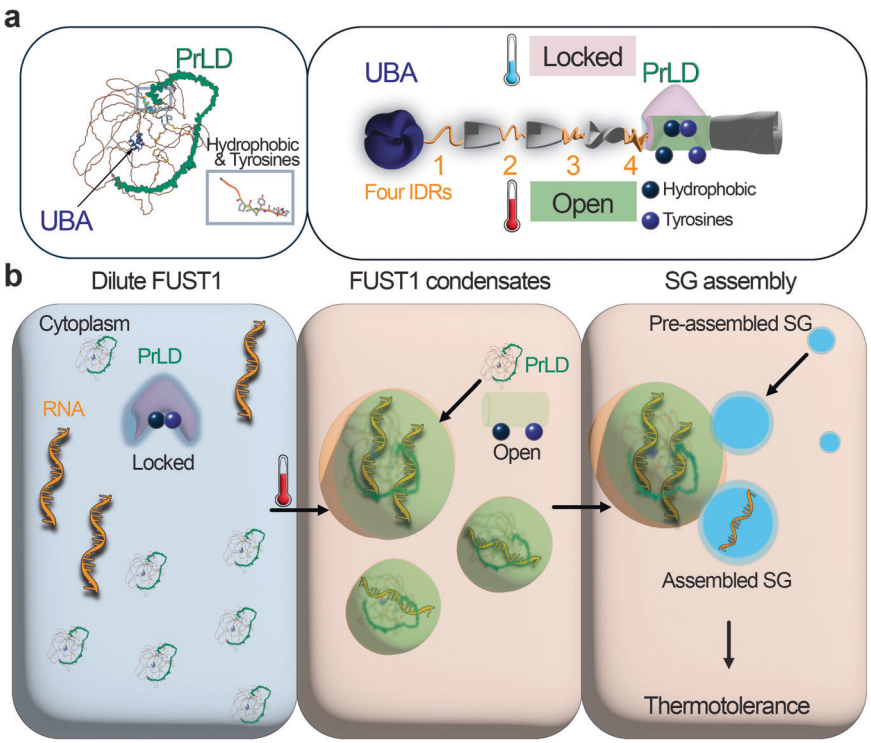

Fig. 1 Temperature-regulated phase behavior of FUST1 promotes SG assembly and thermotolerance. a Domain structure and thermosensitive regulation of FUST1. Left: Schematic of FUST1 (AlphaFold v.3) showing the UBA domain (blue) and PrLD (green), enriched in hydrophobic and tyrosine residues (inset). Right: Linear domain model highlighting four intrinsically disordered regions (IDRs). The temperature-dependent conformational switch of the PrLD between "locked" (inactive) and "open" (assembly-competent) states is shown. The spheres represent the hydrophobic and tyrosine residues that interact with each other, modulating the "locked" state. **b** Model for FUST1-mediated phase separation and its role in SG assembly. Under normal conditions, FUST1 remains diffuse and its PrLD is locked in the cytoplasm, with limited protein and RNA interaction. Upon HS, the PrLD of FUST1 transitions to an open conformation and undergoes phase separation into RNA-containing condensates. These condensates prime SG assembly, contributing to thermotolerance.

Geng et al. advance a conceptual model linking thermosensing and biomolecular condensation in plants, raising exciting questions for future research. N-terminally situated UBA domain is likely the only folded domain in FUST1 (Fig. 1a). Given recent evidence of dramatic ubiquitylation of heat SG components and enhanced activity of SG-resident proteasomes in plants, allowing the degradation of SG components even during the assembly phase,[10] it will be important to determine whether this pathway engages FUST1 for presenting ubiquitylated proteins to the SG-resident proteasomes. It will also be interesting to see whether there is a temperature dependence of RNA binding to FUST1 and/or RNA–FUST1 phase behavior and, more specifically, whether this binding mediates the "lock-to-open" mechanism of FUST1 condensation.

Moving forward, the study by Geng et al. suggests a broader conceptual framework in which autoinhibition and its release — long recognized in signaling proteins[11] — may also represent a widespread strategy among phase-separating proteins. In this regard, it will be critical to examine the extent to which the "lock-to-open" thermo-switch mechanism observed in FUST1 is conserved among other biomolecular condensates that function as environmental sensors.

In the context of plant biology, it remains to be seen whether there is a spatiotemporal hierarchy among the formation of cytoplasmic FUST1 condensates, SGs and several other types of biomolecular condensates known to be induced by heat at different locations within plant cells.[1–5] If such a hierarchy does exist, is it essential for plant fitness under HS — and if so, why?

Finally, the work by Geng et al. invites comparisons beyond plants. Recent findings in yeast and animal cells have shown that phase separation and SG formation are deeply intertwined with cellular stress responses. It is plausible that intrinsically disordered thermosensors bearing structural and functional similarities to FUST1 operate in other kingdoms of life, potentially shaping how cells detect and adapt to a changing environment.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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