A conserved mechanism regulates reversible amyloids of pyruvate kinase in yeast and human cells

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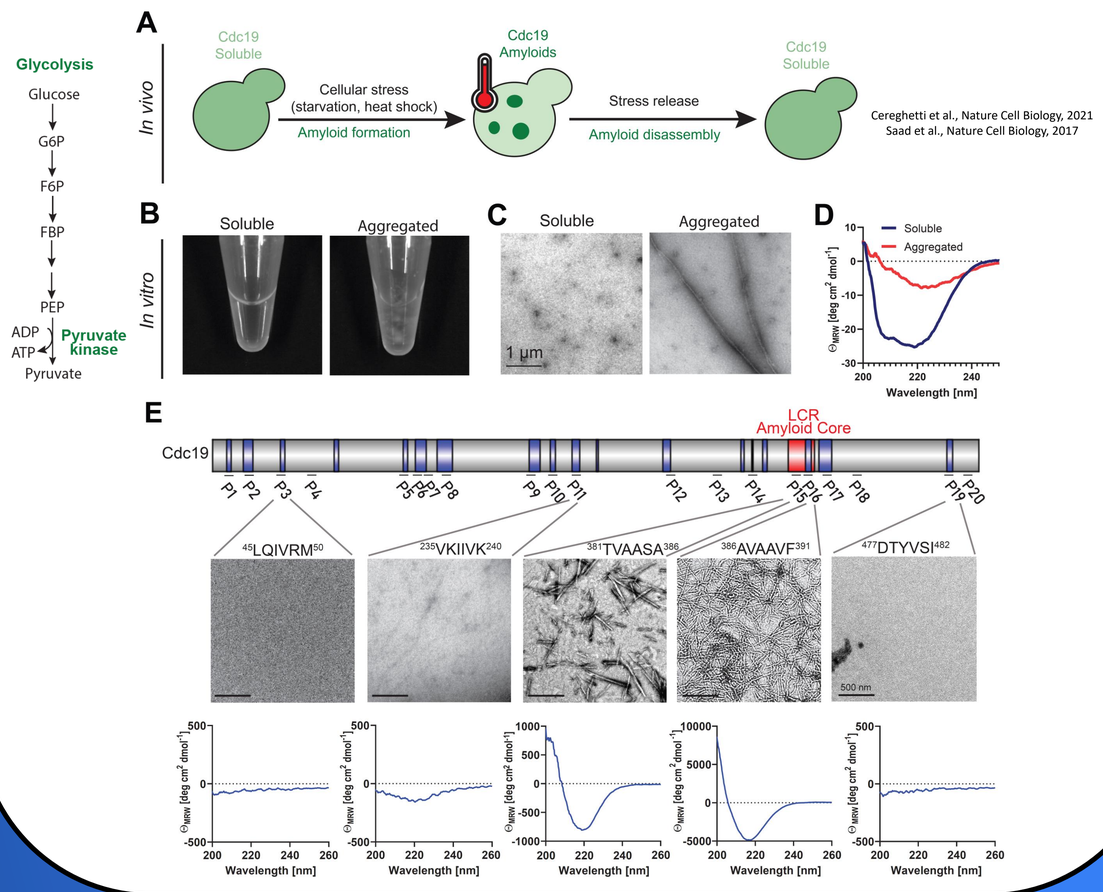
Abstract

- **Amyloids** were long viewed as irreversible, pathological aggregates, often associated with **neurodegenerative diseases**.
- However, **regulated amyloid formation** recently emerged as an important physiological process, which is essential for **adaptive stress responses**.
- Yet, the molecular mechanisms regulating functional amyloids and the differences to their pathological counterparts remained poorly understood.
- Here, we investigate the conserved principles underlying **regulated amyloid formation and disassembly** by studying the essential metabolic enzyme **pyruvate kinase** in yeast (Cdc19) and human cells (PKM2). By combining biochemical and cell biological assays, we demonstrate that pyruvate kinase forms stress-dependent reversible amyloids through a pH-sensitive amyloid core. Stress-induced cytosolic acidification promotes amyloid formation *via* **protonation of specific glutamate** (in yeast) **or histidine** (in human) residues within the amyloid core.
- Our work thus unravels a **conserved and potentially widespread molecular mechanism underlying amyloid functionality and reversibility**.

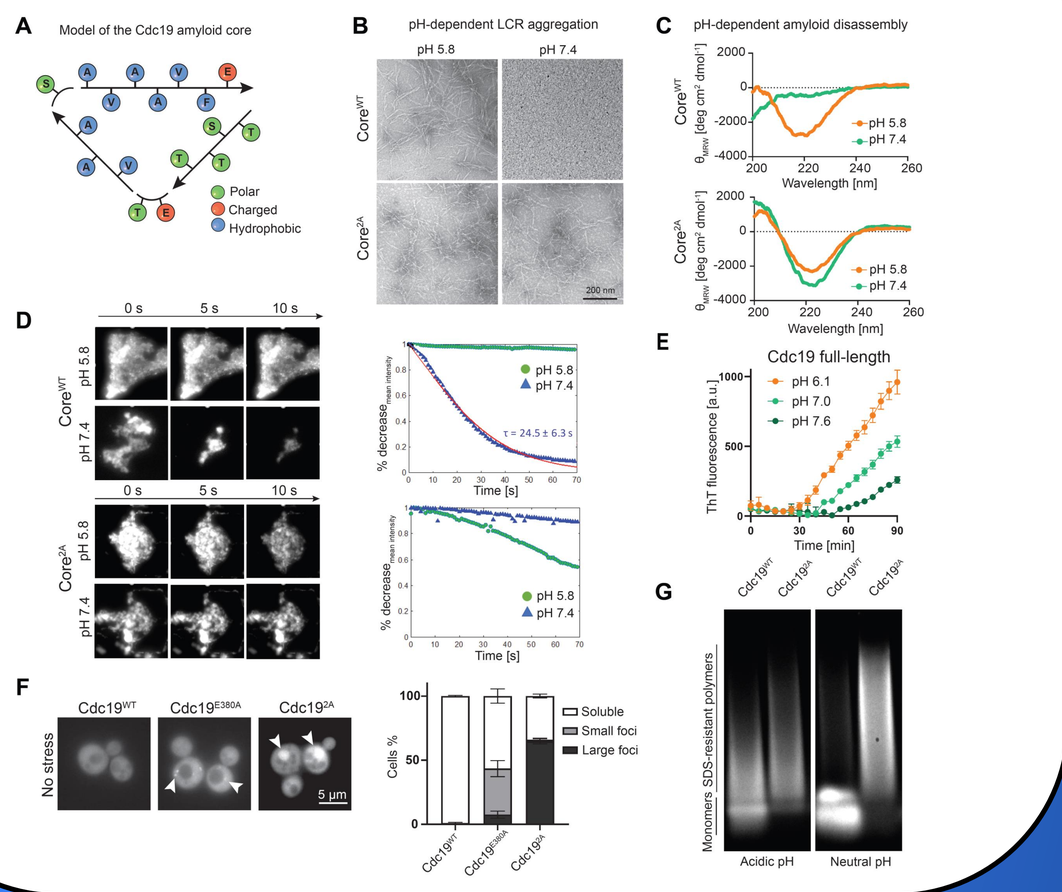
Key questions

- What differentiates **pathological** and **physiological** amyloids?
- What are the **molecular mechanisms** governing the formation and disassembly of functional amyloids?

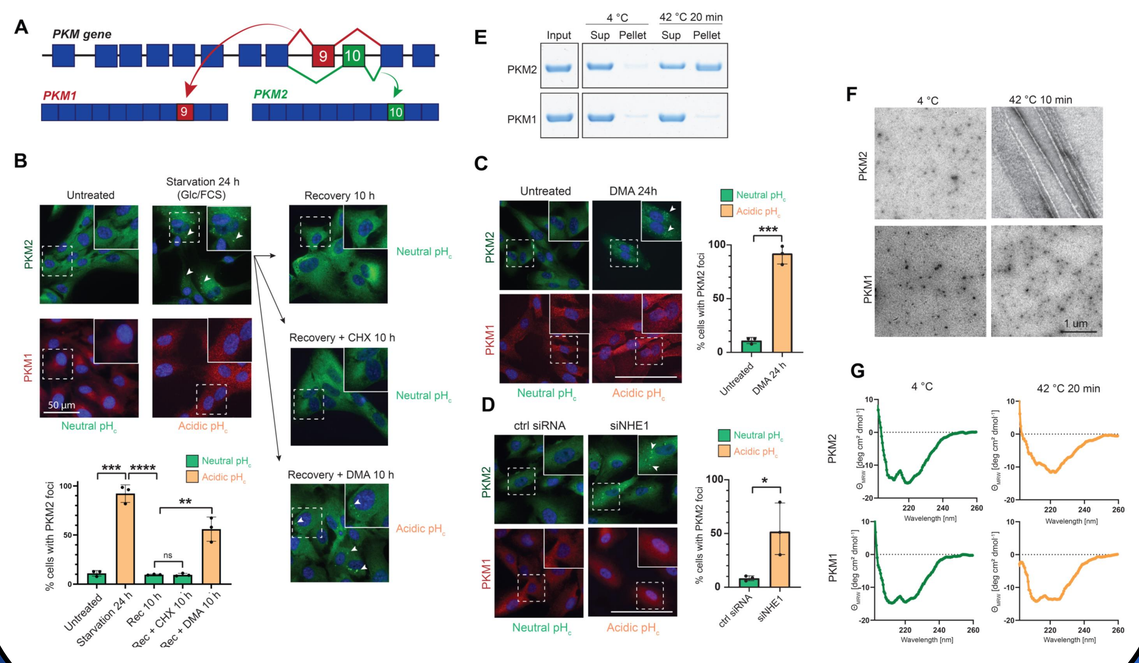
1. Yeast pyruvate kinase (Cdc19) forms functional, reversible amyloids upon stress thanks to an aggregation-prone «amyloid core»



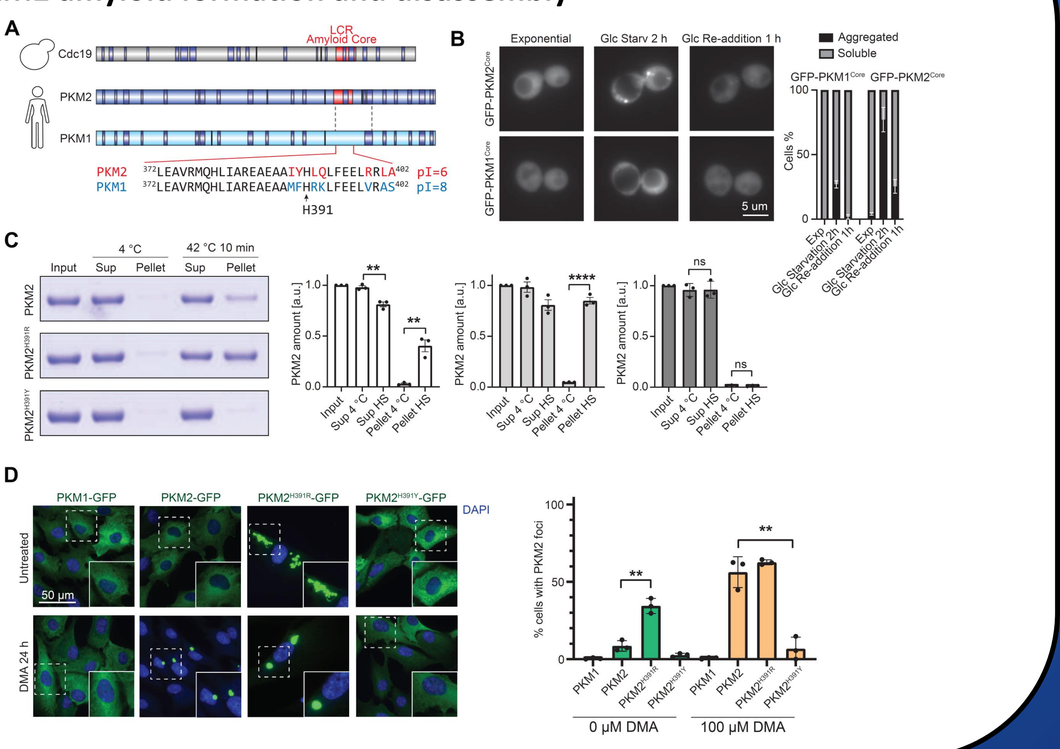
2. Protonation of specific glutamate residues within the amyloid core regulates Cdc19 amyloid formation and disassembly



3. Human pyruvate kinase (PKM2) forms reversible amyloids upon stress-induced cytosolic acidification thanks to an «amyloid core»



4. Protonation of a specific histidine within the amyloid core regulates PKM2 amyloid formation and disassembly



Conclusions and Model – A pH-sensing amyloid on/off switch

1. The essential metabolic enzyme **pyruvate kinase** forms **stress-responsive reversible amyloids**, both in yeast (Cdc19) and human cells (PKM2).
2. Reversible aggregation depends on a conserved **amyloid core**, which is essential and sufficient to control amyloid formation and disassembly.
3. Aggregation is triggered by **cytosolic acidification** & **protonation** of the amyloid core.
4. pH-sensing in yeast is carried out by specific **glutamates**, while in human cells by **histidines**, reflecting the different pH range experienced upon stress by these cells.
5. pH-sensing amyloid cores are a **conserved and potentially widespread mechanism underlying amyloid functionality and reversibility**.