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Protein aggregates: a two-edged sword?

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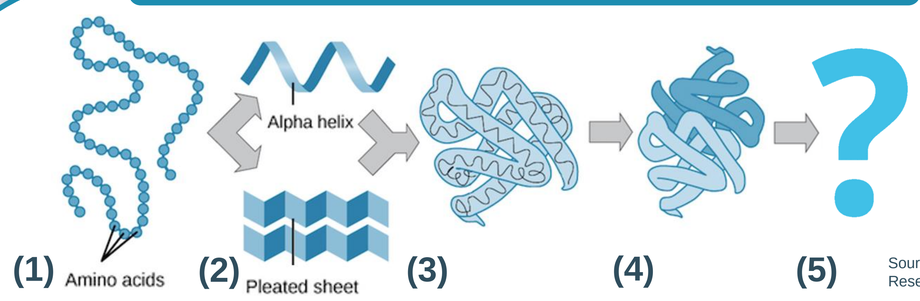
Introduction

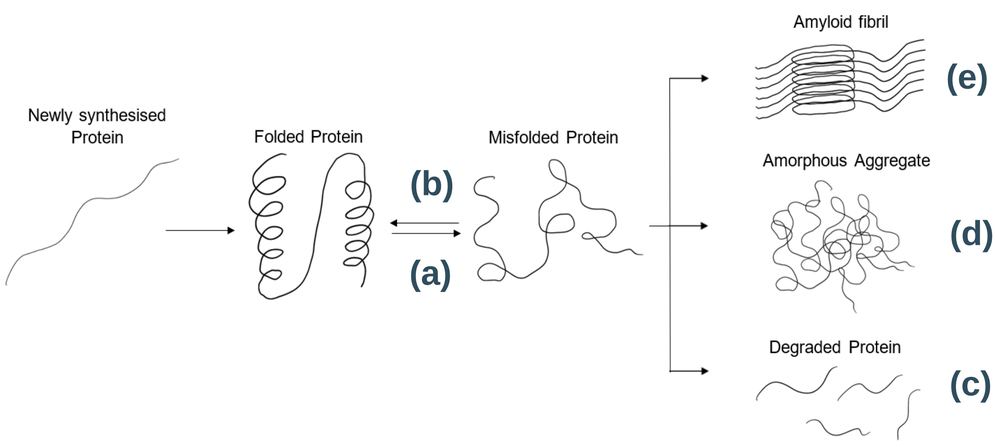
All proteins consist of a primary, secondary and tertiary structure and some proteins can be organised in a quaternary structure and even a **quinary structure**. The first four are well understood, however the fifth, is less known. **Protein aggregates (PAs)** are thought to be a form of quinary structure. PAs arise when proteins misfold and the protein quality control (PQC) system fails. To better understand the underlying mechanisms and aggregate behaviour ***E. coli*** was incubated in six different conditions that induce PAs. Microscopy images were analysed in MicrobeJ to perform in silico **quantitative analysis**.

Quinary structure



Source: National Human Genome Research Institute, 2020

Primary (1), secondary (2), tertiary (3) and quaternary structure (4). Quinary structure (5): Weak associations between multisubunit complexes. Compartmentalization of macromolecules. Influences **protein stability**. Important in **response to stresses.**



Problems while folding to the 3D structure can cause protein **misfolding (a)**. The PQC system **refolds (b)** or **degrades (c)** misfolded proteins to reduce cell damage. If it fails, the misfolded proteins can interact by their exposed hydrophobic domains to form PAs. The two main aggregate types are **amorphous aggregates (d)** and highly **structured amyloid fibrils (e)**.

Consequences of aggregates

Misfolded proteins, and thus PAs, can occur in **stress conditions**, but can also be induced by **genetic mutations** or by the **ageing of the cell**. PAs can have various effects in different cell types.

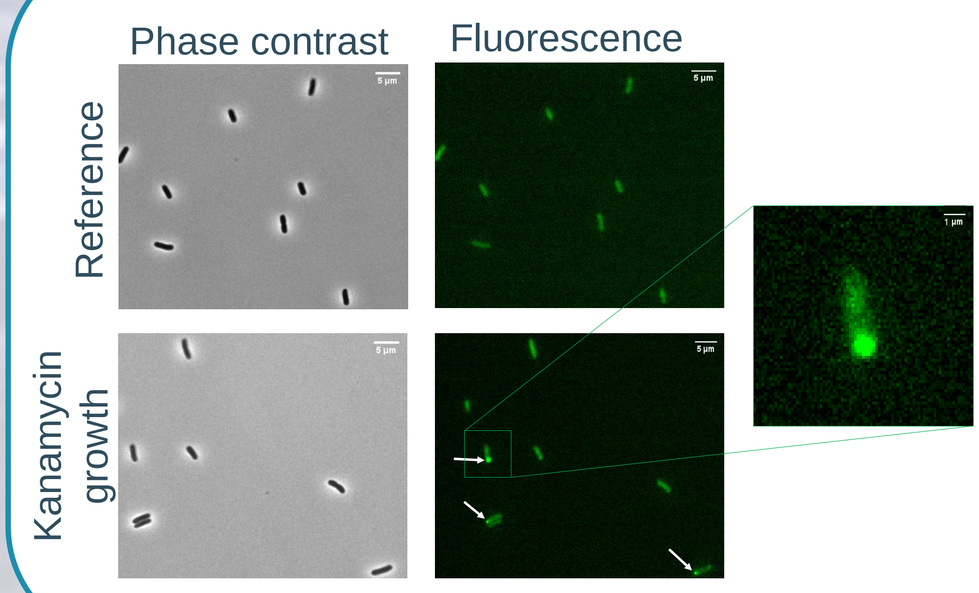
Positive effects

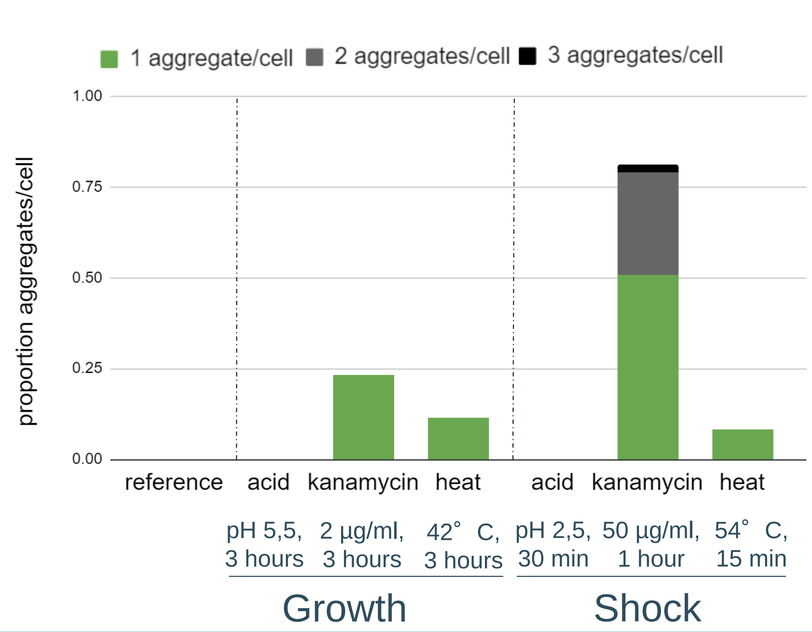
- **Epigenetic memory** in *E. coli*
- Trigger for **dormancy** in *E. coli*
- **Structural PAs**: curli in *Enterobacteriaceae* (cell adhesion)
- **Structural PAs**: chaplins in *Streptomyces coelicolor* (aerial hyphae)
- **Eggshell chorion proteins**: protective amyloid-like structure in insects and fish

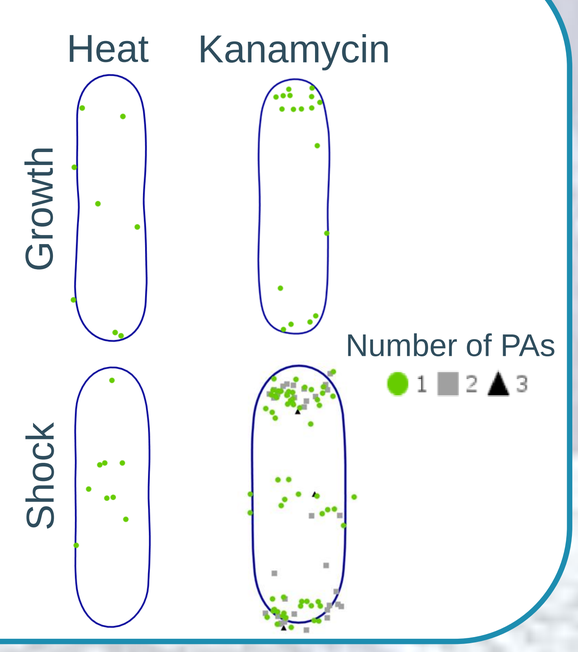
Negative effects

- Reduction of permeability of the **plasma membrane** in all organisms
- **Loss-of function diseases**: ALS, cystic fibrosis and Fabry disease in humans
- **Amyloids**: neurodegenerative diseases (Alzheimer's disease) in humans
- **Prions**: Creutzfeldt-Jakob disease in humans

Experiment







Conclusion

The proportion of stress-induced PAs per cell varies per condition. The **kanamycin shock** showed an average of **0.81 PAs/cell**, which was significantly higher than the other conditions. A possible explanation is that kanamycin induces intrinsic faults in the protein sequence, which causes **irreversible misfolding**. Concerning subcellular localisation, the **heat shock** showed PAs more towards the **centre of the cell**, as opposed to at the cell poles as detected in the other conditions. The central localisation could be due to the **short time** the PAs had to diffuse.

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