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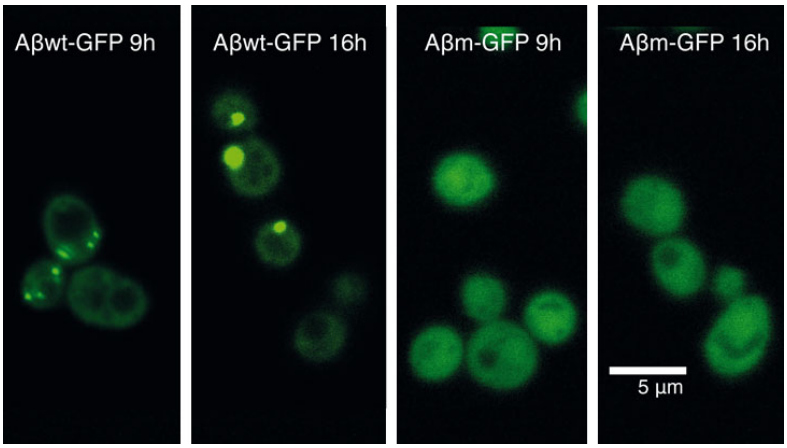
Cellular Response to Protein Misfolding



Protein misfolding and aggregation is associated with numerous degenerative human disorders such as type-II-diabetes or Alzheimer's disease. In previous research we identifieda threshold abovewhich a cell began to actively accumulate protein aggregates. The data obtained in this new research confirms that the formation of these aggregates is an energetically expensive process for the cell, but it can protect it against the harmful effects associated with misfolded proteins.

The model proteins studied have different distribution in yeast. Abeta(wt)-GFP after 9 and 16 h of induction is accumulated into foci. Whereas, Abeta(mut)-GFP after 9 and 16 h of induction remains diffusively distributed.

Protein misfolding and aggregation is associated with numerous degenerative human disorders such as type-II-diabetes or Alzheimer's disease. Despite this, aggregation prone proteins seem to be conserved in all kingdoms of live. In fact, there is an increasing number of examples in which cells exploit protein aggregates for functional purposes, from scaffold the melanin in the skin to memory storage. Consequently, during evolution cells have developed different strategies to tolerate and control the protein aggregation process, such as control the protein expression or chaperones to facilitate a correct protein folding.

One of the main research lines of our group is study the misfolding and aggregation of disease-related proteins. We study this phenomenon from a biophysics point of view to know the properties involved in this event but also using *in vivo* models to understand its relationship with diseases and cellular functions.

As a first attempt to unravel how cells response against protein misfolding, we recently expressed 20 GFP-fused peptides covering a continuous range of aggregation propensities. We derived these peptides from the amyloid-β-peptide (Aβ42) (associated to Alzheimer disease) and expressed them in yeast. Interestingly, despite that most of these peptides are highly insoluble, just some of them are recruited into foci. With this approach, we identified an aggregation propensity threshold above which the cell actively accumulates a protein into foci.

Now, we have used two proteins from this collection, which are located on either side of the aggregation threshold, to decipher why protein foci are or are not formed in cells. Specifically, we have characterized how these two proteins impact on cell fitness and cellular homeostasis.

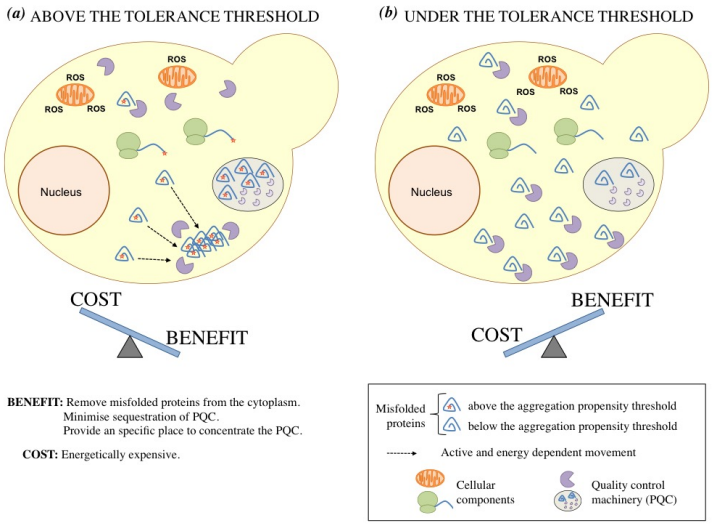


Figure 2: One unfolded protein response: two strategies to control the toxic effects. Model showing the different benefits and costs of accumulating a misfolded protein into foci. Specifically, this diagram shows two proteins, mostly insoluble, but located either side of an aggregation threshold above which the cell actively recruits a protein into foci [11] (a). This process could offer benefits but it is also energetically expensive (cost). Under the threshold, the protein remains diffuse through the cytoplasm (b). This could favour the formation of harmful interactions that could initiate a cascade of misfolding and oxidative stress. ROS, reactive oxygen species.

Our results support that the formation of inclusion bodies is an energetically expensive process that protects the cell against harmful effects associated with misfolded proteins, including oxidative stress. We suggest that levels of oxidative stress may serve as a trigger for protein recruitment into foci. Overall, our data indicates that the cellular response to protein misfolding is able to discern and accommodate the specific properties of polypeptides (e.g. aggregation propensity).

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