Evolution of Robustness to Protein Mistranslation by Accelerated Protein Turnover

Dorottya Kalapis[1], Ana R. Bezerra[2], Zoltán Farkas[1], Peter Horvath[1], Zoltán Bódi[1], Andreea Daraba[1], Béla Szamecz[1], Ivo Gut[3], Mónica Bayes[3], Manuel A. S. Santos[2*], Csaba Pál[1*]

The accuracy of protein synthesis is fundamental to ensure healthy living of all organisms. For this reason, it is generally assumed that protein synthesis fidelity is maintained at very high levels at all times. However, recent studies show significant degradation of protein synthesis accuracy (mistranslation) under nutrient starvation, diseases and aging conditions. These observations raise several questions. For example, how do cells sustain continuous synthesis of aberrant proteins? how does accumulation of aberrant proteins alter cell physiology? do aberrant proteins aggregate in the cell? how do cells eliminate such aberrant proteins? To answer some of these questions Manuel Santos and his iBiMED´s colleagues and Csaba Pal at the Hungarian Academy of Sciences designed a long term (over 250 generation) experiment to follow the evolution of tolerance and adaptation of cells to continuous synthesis of aberrant proteins.

Aberrant proteins produced large intracellular clumps and had a marginal effects on cell viability, suggesting that, conversely to common thinking, protein aggregates per se may not kill the cell. More surprisingly, cells adapted very fast to accumulation of aberrant proteins and were able to erase protein clumps very efficiently.

They did so by rearranging their genome at fast rate, boosting protein synthesis, degradation and energy consumption (glucose consumption) rates. In other words, accumulation of aberrant proteins may not kill the cell but has major impact on homeostasis and physiology. It also pushes cells to the verge of energetic collapse. The iBiMED team is now trying to figure out if these data are relevant to better understand the molecular basis of aging and degenerative diseases.

1 — Synthetic and Systems Biology Unit, Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Szeged, Hungary
2 — Department of Medical Sciences & iBiMED, University of Aveiro
3 — Centro Nacional de Análises Genómico, Parc Científic de Barcelona, Spain

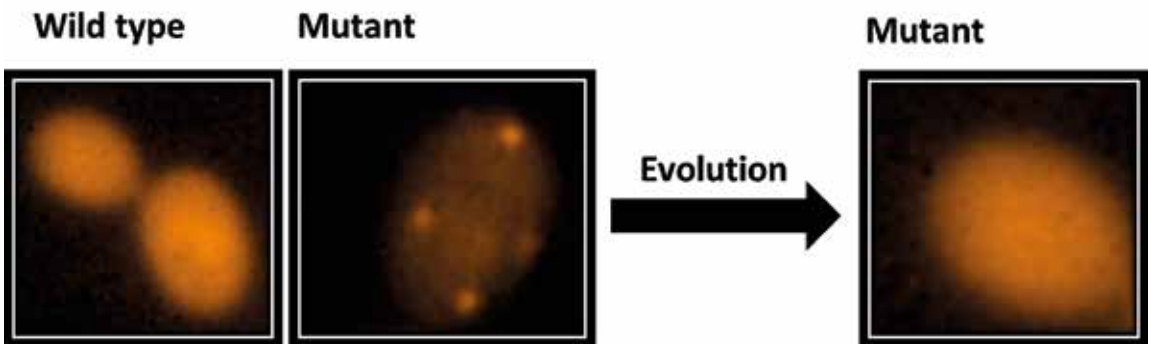

FIGURE 1
The figure shows a yeast wild type cell stained with a fluorescent sensor of protein aggregation (left panel). In this WT cell proteins are synthesized correctly and do not aggregate, resulting in even distribution of fluorescence in the entire cell. The mutant cell (middle panel) production of proteins with high level of errors leads to their aggregation in specific locations in the cell (fluorescent foci). Cells survive and adapt rapidly to the presence of protein aggregates and are able to erase them during evolution, as indicated by the even distribution of the fluorescent sensor in the evolved Cell (right panel).