Talk

Study of the role of importin alpha Imp1 in the heat shock response

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Keywords: Importin; Heat stress; heat shock response; Chaperones; Nucleus

ABSTRACT

Motivation: Protein homeostasis or proteostasis is essential for cellular survival and tissue homeostasis. Cellular proteostasis is maintained by a tight balance between protein synthesis, folding and degradation. Various stress conditions, mutations, translation defects, etc. can disrupt this balance, leading to the accumulation of misfolded proteins prone to aggregation, a hallmark of several human diseases [1]. In this situation, cells activate the heat shock response (HSR), a transcriptional response driven by the universal transcription factor Hsf1, which upregulates molecular chaperones to counteract folding stress [2]. Among these chaperones, Hsp104 plays a key role in disaggregating misfolded proteins, promoting their refolding or degradation. However, the mechanisms regulating Hsp104 subcellular localization remain poorly understood. Previous results from the laboratory have shown that in the absence of Importin alpha Imp1, which functions in nucleocytoplasmic transport, the cellular distribution of the chaperone disaggregase Hsp104 is altered [3].

Methods: In this work, we used a combination of live-cell fluorescence microscopy and genetic analysis to characterize the role of Imp1 in the regulation of Hsp104 nucleocytoplasmic transport and its contribution to cellular proteostasis under folding stress conditions.

Results: Our results show that, in the absence of Imp1, nuclear levels of Hsp104-GFP are significantly reduced compared to wild-type cells and it is accumulated in nuclear foci or aggregates under non-stressed conditions. Upon heat stress, Hsp104 nuclear levels further decrease in imp1Δ cells, correlating with an impaired stress response and reduced cellular fitness. Currently we are testing whether Imp1 is required for the nuclear localization of other HSR chaperones as part of a general mechanism to maintain nuclear proteostasis in unperturbed conditions and upon folding stress.

Conclusions: Our findings demonstrate that Importin-α Imp1 is required to maintain cellular fitness upon folding stress through the regulation of Hsp104 nucleocytoplasmic transport..

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