Studies on prokaryotic and eukaryotic ribosomes and their interaction with unfolded proteins

Abstract

Ribosome is the cellular translational machinery with the primary function of protein synthesis. It also exhibits a non-canonical, ATP-independent chaperoning activity, in its non-translating state. This activity can be crucial for cell survival under stress, when the ATP-dependent chaperones are incapacitated. The chaperoning activity is expressed when the unfolded protein is present at stoichiometric concentration with respect to the ribosome. However, a 5-fold excess concentration of unfolded protein acts as an anti-association factor resulting in sustained ribosomal subunit dissociation and degradation. Under stressful conditions, like those prevailing during the stationary phase, global unfolding of the proteome can make the cellular ribosomal population vulnerable to unfolded protein-mediated dissociation and degradation. The phenomenon of ribosome hibernation is a predominant survival strategy employed by prokaryotic bacterial cells, which entails maintenance of the ribosome in a translationally silent state. Stress factors like the hibernation promoting factor (HPF) are expressed in both gram-positive and gram-negative bacteria, which can associate with the ribosome and preserve them in monomeric factor-bound 70S or dimeric 100S hibernating states. Our studies, discussed in **Chapter 2**, demonstrate that such ribosomal structures are resistant to unfolded protein-mediated subunit dissociation and degradation and retain their ATP-independent chaperoning activity.

Previous studies in our laboratory demonstrated that super-stoichiometric presence of aggregating proteins, like the amorphously aggregating lysozyme and the amyloid forming Alzheimer's disease (AD) associated human Tau protein (both, the full length Ht40 and its microtubule binding subdomain, K18), in the vicinity of the ribosome can lead to co-aggregation of the ribosomal components. Deposition of extraneuronal amyloid β (Aβ) plaques is another marker of AD and Aβ peptides can also accumulate and oligomerize intraneuronally. The studies discussed in **Chapter 3** demonstrate that the aggregating Aβ peptides, both Aβ 1-40 and Aβ 1-42, can engage with rRNA-rich eukaryotic ribosomal surface which can lead to stimulation of their aggregation and loss of physical integrity of the ribosome and formation of rRNA-protein co-aggregates. This is favoured at a low RNA or low ribosome stoichiometry, with respect to the protein which could be mitigated by polyphenolic inhibitors of amyloid aggregation. Hence, Aβ aggregates might mediate their AD-associated neurotoxicity by destabilizing the ribosomal population in AD-afflicted neurons.

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