Dynamics of the Nascent Polypeptide-Associated Complex in the Ribosomal Exit Tunnel

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In all known life, proteins are synthesized on ribosomes. This delicate biochemical process is regulated by a multitude of factors, one of them being the Nascent-polypeptide Associated Complex (NAC) in Eukaryotes. NAC monitors a nascent chain (NC) within the ribosomal tunnel, ensuring its protection, ideal folding conditions, and subsequent targeting within the cell. NAC docks near the tunnel exit and interacts with emerging NCs. In one of the binding scenarios, NAC inserts one of its termini deep into the tunnel until it reaches a short NC. However, the mechanistic insights and driving forces behind this process remain unclear. We address the molecular mechanism of this insertion using molecular dynamics simulations. Pulling simulations of a Homo sapiens ßNAC N-terminal segment comprising of 24 residues (WT) inside the ribosomal exit tunnel were performed in an explicit aqueous environment. In silico mutations of two key arginine residues (R2A) enabled the identification of a potential motif facilitating the tunnel insertion. The comparison of WT and R2A was based on pulling force, electrostatic interactions, and solvation effects. Based on our results, we have identified a novel, evolutionarily conserved arginine-rich motif and propose its mechanistic significance. Documented somatic mutations of the identified arginine motif have been associated with cancer - Adenomas and Adenocarcinomas or Squamous cell neoplasms. Our study expands the knowledge about the birthplace of proteins, contributing to research into prevention and treatment of misfolding-related diseases. Further research could investigate the dynamics of NAC in the ribosomal tunnel of a different organism or its interactions with misfolded proteins in the cytosol, as observed during metabolic stres

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