Multistate GTPases Control Cotranslational Protein Targeting

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Abstract

The cotranslational protein targeting process transports roughly one-third of proteins in a cell's genome from the cytoplasmic space to the membrane compartments. This process is regulated by the signal recognition particle (SRP) and its receptor (SR). I aim to understand how the complex assembly and activation of GTP hydrolysis during the SRP-SR interaction are controlled so that the SRP machinery functions as a molecular switch to regulate the series of molecular events in space and time. Using a combination of biochemical and biophysical approaches, this dissertation has defined the kinetic and thermodynamic framework of the SRP-SR interaction and has elucidated the regulatory role of the SRP-SR interaction on the protein targeting process. In particular, this dissertation demonstrates that the function of the SRP machinery is governed by a series of ordered conformational changes during SRP-SR interaction that culminate in their activation of GTP hydrolysis. Further, these conformational changes closely monitor and actively respond to the biological cues so that they provide discrete control points at which regulation can be exerted on the protein targeting reaction spatially and temporally. The paradigm provided in this dissertation offers a mechanistic view of another fascinating system in which multistate protein machineries control critical biological processes with exquisite order.

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