Learning from natural molecular machines: the artificial chaperonin

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Incorrect folding of proteins in living cells may lead to malfunctioning of the cell machinery. To prevent such cellular disasters from happening, all cells contain molecular chaperones that assist nonnative proteins in folding into correct native structure. One of the most studied chaperone complexes is the GroEL-GroES. The GroEL part has a “double-barrel” structure, which consists of two cylindrical chamber joined at the bottom in a symmetrical fashion. The hydrophobic rim of one of the GroEL chambers captures nonnative proteins. The GroES part acts as a lid that temporarily closes the filled chamber during the folding process. Several capture-folding-release cycles are required before the nonnative protein reaches its native state. Here we report molecular simulations that suggest that translocation of the nonnative protein through the equatorial plane of the complex boosts the efficiency of the chaperonin action. If the target protein is correctly folded after translocation, it is released. However, if it is still nonnative, it is likely to remain trapped in the second chamber, which then closes to start a reverse translocation process. This shuttling model provides a natural explanation for the prevalence for double-barreled chaperonins. Moreover, we argue that internal folding is both more efficient and safer than a scenario where partially refolded proteins escape from the complex before being recaptured. Based on these results we propose a design for a device to help single protein refold and cluster break down.