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# A model of threshold behavior reveals rescue mechanisms of bystander proteins in conformational diseases

Conformational diseases result from the failure of a speci

c protein to fold into its correct functional state. The misfolded proteins can lead to the toxic aggregation of proteins. Protein misfolding in conformational diseases often displays a threshold behavior characterized by a sudden shift between non-toxic to toxic levels of protein misfolds. In some conformational diseases, evidence suggest that misfolded proteins interact with bystander proteins (unfolded and native folded proteins), eliciting a misfolded phenotype. These bystander isomers would follow their normal physiological pathways in absence of misfolded proteins. In this paper we present a general mechanism of bystander and misfolded protein interaction which we have used to investigate how the threshold behavior in protein misfolding is triggered in conformational diseases. Using a continuous flow reactor model of the endoplasmic reticulum, we found that slight changes in the bystander protein residence time in the endoplasmic reticulum or the ratio of basal misfolded to bystander protein in ow rates can trigger the threshold behavior in protein misfolding. Our analysis reveals three mechanisms to rescue bystander proteins in conformational diseases. The results of our model can now help direct experiments to understand the threshold behavior and develop therapeutic strategies targeting the modulation of conformational diseases.