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Membrane-mediated Structural Regulation of Adam10 During Efferocytosis.

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Protein of a disintegrin and metalloproteinase (ADAM) family are responsible for the shedding of membrane-proximal extracellular domains (ECDs) of various membrane proteins. The removal of ECDs is involved in numerous biological processes, including e.g. cell migration, immune cell recruitment or macrophage activation. In the context of efferocytosis, previous studies showed that the ADAM10 protein shedding activity is triggered in apoptotic cells by the externalisation of phosphatidylserine (PS) lipids. Yet the molecular determinants of this activation are not well understood.

Structures experimentally observed show a closed and open form of ADAM10, suggesting that the opening of the protein is instrumental for its activity. By using adaptive sampling, and Markov-state models, we studied the opening process of ADAM10 in presence and absence of PS lipids in the membrane. We discovered that ADAM10 presents open structures even without the presence of POPS, suggesting a basal activity, which was confirmed experimentally. We could show that there is a shift in structural states, favoring open states in presence of POPS coherently with the behaviour observed experimentally. This behaviour is explained by the capture of the Cysteine-rich domain by the membrane in presence of POPS, a behaviour observed in other members of the ADAM family.