Title

Guanidinium-Rich ROMP Polymers Drive Phase, Charge, and Curvature-Specific Interactions with Phospholipid Membranes

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Abstract

Protein transduction domains (PTDs) and their and their synthetic mimics are short sequences capable of unusually high uptake in cells. Several varieties of these molecules, including the arginine-rich Tat peptide from HIV, have been extensively used as vectors for protein, DNA, and siRNA delivery into cells. Despite the wide-ranging utility of PTDs and their mimics, their uptake mechanism is still under considerable debate. How the molecules are able to cross phospholipid membranes, and what structural components are necessary for optimal activity are poorly understood. This thesis explores how PTDMs interact with phospholipid membrane phase, anionic lipid content and negative Gaussian curvature generation along the structural variables of polymer length, charge density, hydrophobicity, aromaticity, and architecture. From these it is demonstrated that PTDM-membrane interaction is primarily controlled by balancing solubility of polymer in solution and in the lipid. Barriers to activity, such as anionic lipid content and membrane rigidity, can be overcome by the addition of hydrophobicity, but this has to be balanced by considerations of water solubility and toxicity.

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