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Mechanisms of protein transduction domains: HIV TAT and ANTP penetratin as prototypical cases ABHIJIT MISHRA, University of Illinois, Department of Materials Science and Engineering, NATHAN SCHMIDT, University of Illinois, Department of Physics, VERNITA GORDON, University of Illinois, Department of Materials Science and Engineering, GERARD WONG, University of Illinois, Department of Materials Science and Engineering, Department of Physics — Biologically active molecules such as proteins and oligonucleotides can be transduced across cell membranes with high efficiency when covalently linked to a Protein Transduction Domain (PTD), such as the TAT domain in the HIV virus and ANTP from the fruitfly. All PTDs have a high content of basic amino acids resulting in a net positive charge. Electrostatic interactions between cationic PTDs and the negatively charged phospholipids that constitute the plasma membrane are likely to be responsible for peptide uptake, but no detailed structural studies exist. We examined membrane structures induced by the cationic TAT domain and those induced by other cationic polypeptides as a function of membrane composition using synchrotron x-ray scattering. We find that both the TAT PTD and ANTP generate negative Gaussian curvature, which is necessary for pore formation, and produce a bicontinuous Pn3m double diamond cubic phase. A general mechanism is proposed.

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