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Targeting the endosomal membrane by biomimetic, pH-sensitive polymers

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The interaction of biomimetic polymers with membranes of various lipid compositions can cause a variety of physical-chemical membrane perturbations. These can be exploited to damage or overcome membranes in the context of drug delivery, e.g. assisting endosomal escape. The lowering of the endosomal pH, and the occurrence of the negatively charged lipid BMP during endolysosomal development, can be used to selectively permeabilize endosomal membranes.

For a rational design and selection of suitable polymers for drug delivery applications, we need to understand the underlying membrane biophysics. We investigate the principles of pH-sensitive activity and selectivity of membrane-active polycations.

The polymer pKa, pH, and lipid composition are systematically varied to reveal the network of membrane perturbation mechanisms under conditions representing cytoplasmic or early/late endosomal membranes. Membrane leakage, electrostatic lipid clustering (the local enrichment of negatively charged lipids by positively charged polycations), and membrane fusion can play important roles for membrane permeabilization. Using fluorescence and monolayer methods as well as microcalorimetry, we characterized membrane perturbations caused by the polymers. These interactions were examined using different membrane models like large and giant unilamellar vesicles, multilamellar vesicles and lipid monolayers.

We find that the pH sensitive polymers do not insert into the lipid membrane, but rather induce local heterogeneities, as well as limited membrane permeabilization. Our data indicates that the polymers interact electrostatically especially with negatively charged, i.e. endosomal-like, model membranes.

This dominance of polymer and membrane charge underlines the role of the negatively charged endosomal lipid BMP, while the pH change contributes indirectly to endosomal escape by increasing the polymer charge.