

P008 Understanding histidine rich amphipathic peptide mediated gene delivery using solid-state NMR techniques

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The histidine rich amphipathic peptide LAH4 is an efficient DNA vector which also has interesting antibiotic capabilities. The interaction of this peptide with biological membranes is a key determinant of its activity. We have used solid-state NMR methods to characterise the structural topology and quantify the membrane disruptive effects of the peptide in mixed model membranes. We show that the peptide interacts preferentially with anionic lipids and destabilises the lipid acyl chains in model membranes in its active conformation at acidic pH but not at neutral pH. Our model for peptide mediated disruption of the endosomal membrane during endocytosis is in agreement with models derived from recent computer simulations of the membrane interaction of related antibiotic peptides that form disordered toroidal pores. In a further step, we relate the biophysical data to the *in vitro* transfection efficiency of various mutant peptides and identify an important role for anionic lipids during endosomal acidification. We conclude that the biophysical understanding of the peptide activity can be used in the design of improved vector peptides whilst providing important information about the mechanism of amphipathic peptide mediated gene transfer.