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Surface Adsorption of Protein Corona Controls the Cell Internalization Mechanism of Multicomponent Lipoplexes in Serum

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Designer multicomponent lipoplexes have recently emerged as especially promising transfection candidates, since they are from 10 to 100 times more efficient than binary complexes usually employed for gene delivery purposes. Here, we show, for the first time, that after internalization binary complexes of lower transfection potency remain in compact perinuclear endosomes, while multicomponent systems have intrinsic endosomal rupture properties that allow plasmid DNA to escape from endosomes with extremely high efficiency. Endosomal rupture results in an extraordinarily homogeneous distribution of unbound plasmid DNA throughout the cytoplasm and in the nucleus. Serum has often been reported as a barrier to efficient lipid-mediated transfection. Here we found that the transfection efficiency of multicomponent lipoplexes increases in serum. To provide insight into the mechanism of lipoplex-serum interaction, several state-of-the-art methodologies have been applied. The nanostructure of lipoplexes was found to be serum-resistant as revealed by high resolution synchrotron small angle X-ray scattering, while dynamic light scattering measurements showed a marked size increase of complexes. Proteomics experiments showed that serum proteins competed for the cationic surface of lipid membranes leading to the formation of a rich a 'protein corona'. Combining structural results with proteomics findings, we suggest that such a protein corona can promote large aggregation of intact lipoplexes. According to a recently proposed size-dependent mechanism of lipoplex entry within cells, protein corona-induced formation of large aggregates most likely results in a switch from a clathrin-dependent to caveolae-mediated entry pathway into the cells which is likely to be responsible for the observed transfection efficiency boost. As a consequence, we suggest that surface adsorption of protein corona can have a high biological impact on serum-resistant cationic formulations for in vitro and in vivo lipid-mediated gene delivery applications.