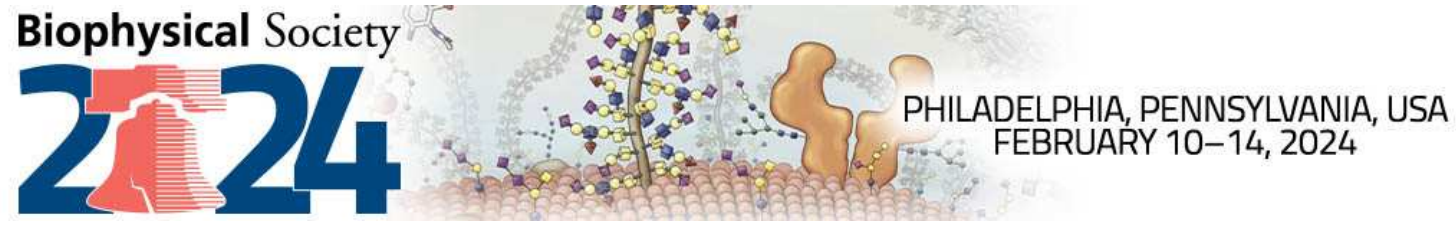

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FUSOGENICITY OF CATIONIC LIPOSOMES WITH PHASE-SEPRATING MULTICOMPONENT LIPID COMPOSITIONS

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Abstract:
Cationic lipids such as 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) have increasing applications in liposomal vehicles used for delivery of variety of cargos and nucleic acids. While the mechanism of cargo delivery by such cationic liposomes remains a subject of debate, it has been proposed that positive charge of these liposomes leads to their attraction towards cell membranes where they next adhere and then fuse, leading to the release of their cargo into cytoplasm. While high concentration of cationic lipids is often required for high efficacy, it raises concerns of potential toxicity, highlighting the need for finding a balance. This study explores the use of membrane phase separation to control the distribution of cationic lipid DOTAP on the surface of liposomes with the goal of tuning their fusogenicity. To this end, ternary lipid mixture of DOPC:DPPC:Chol, at different molar ratios, was used to prepare nano-scale phase-separating liposomes and cationic DOTAP was incorporated into these liposomes. Level of fusogenicity of different phase-separating cationic liposomes, with the same amount of DOTAP, was then examined by monitoring their fusion into micron-sized liposomes as model target membrane using fluorescence microscopy. The results suggested that increasing local concentration of DOTAP via phase separation can enhance the fusogenicity of cationic liposomes and that this effect was strongest in the phase-separating formulation that provided the highest local DOTAP concentration among the examined compositions. These experimental studies were further complemented with computation modeling based on a surface Navier-Stokes-Cahn-Hilliard phase-field model that we previously reported for prediction of phase-behavior in multi-component membranes and was further advanced here to account for electrostatic interactions. Results of computational modeling showed good agreement with those from above-mentioned experiments. Together, findings of this study can be utilized for the design of highly fusogenic cationic delivery liposomes with minimal toxicity.

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