Exploring the Mechanism of Endosomal Escape of Lipid Nanoparticles: A Coarse-Grained Molecular Dynamics Study

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We illustrate here our recent application study of our quantitative coarse-grained model; SPICA force field, to the endosomal escape mechanism of lipid nanoparticles(LNPs). LNPs are one of the most promising non-viral gene delivery carriers. LNPs have recently been employed in COVID-19 mRNA vaccines and are expected to have applications in cancer therapy and regenerative medicine. LNPs administered to the body enter the cell by endocytosis. Nucleic acids must be released into the cytoplasm before they are degraded by a drop in pH in the endosome (transfection), but in many cases only a few percent are released. The molecular mechanism is still illusive because it occurs at the nanoscale. Therefore, clarification of this phenomenon through molecular dynamics (MD) simulations will enable more effective design of LNPs with high drug release efficiency. In this study, a series of large-scale coarse-grained MD simulations of LNPs fusing to endosomal membranes has been performed using the SPICA force field. In particular, the fusion mechanism of LNPs with the endosomal membrane was examined in the context of the efficiency of the endosomal escape. We would also like to show the performance of the SPICA force field for this complex system including a variety of lipids, sterols, and nucleic acids.