

DNA-enabled PEG reduction in Lipid Nanoparticles

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PEG-lipid is an essential component of lipid nanoparticles (LNPs), providing steric shielding and influencing overall delivery efficiency. Several clinically approved nucleic-acid LNPs contain around 1.5 mol% PEG-lipid, an amount that reflects the trade-off between colloidal stability and effective membrane interactions [1]. However, repeated administration induces anti-PEG antibodies and accelerated blood clearance [2, 3]. Reducing PEG is therefore desirable, but it may also alter the protein corona of LNPs. Previous work showed that surface DNA and human plasma proteins can organize LNPs into a multicomponent bionanoarchitecture, reducing immune-cell uptake and monocyte/macrophage sequestration [4]. Building on this finding, we characterized how the protein corona responds to a PEG-lipid reduction from 1.5 to 0.5 mol% in cationic pDNA-LNPs, with and without surface DNA.

When compared at matched particle number, PEG reduction increased plasma protein association with bare LNPs, and proteomic analysis showed changes in the relative composition of the corona. DNA-coated LNPs behaved differently. Their protein corona was more conserved across the two PEG conditions, and overall protein association was lower than that observed for the corresponding bare LNPs.

These results indicate that DNA coating makes the LNP surface less available for protein adsorption, even when PEG content is reduced, partially compensating for the lower PEG surface coverage. These interfacial differences are expected to influence cellular recognition, immune-cell interactions, and biodistribution, and ongoing studies are aimed at establishing the extent and mechanisms of these effects.

References

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