sHDL Remodeling: Impact of Lipid Composition, Acyl Chain Length, Charge, and Cholesterol Content

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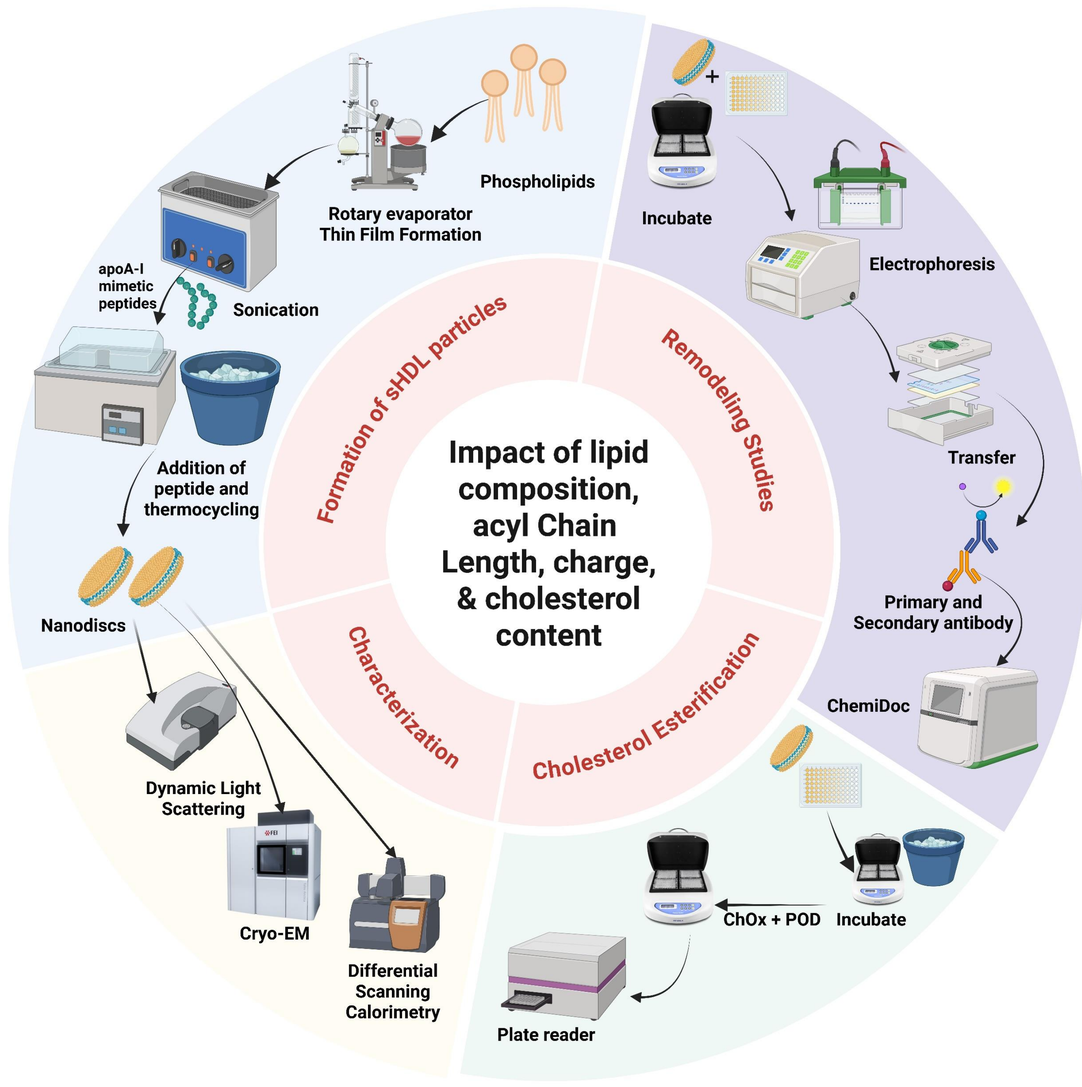
1. Introduction

- **HDL-mimicking nanodiscs (sHDL)** promote cholesterol efflux from macrophages, but cardiovascular benefits maybe limited by downstream **RCT** steps which are rate-limiting.
- A key bottleneck is **LCAT-mediated cholesterol esterification**, which promotes HDL maturation from **discoidal to spherical** forms.
- sHDL can also **remodels endogenous HDL** by displacing apoA-I, generating **lipid-poor pre-beta HDL species** that are potent cholesterol acceptors.
- The lipid composition of sHDL, including **phospholipid acyl chain length, surface charge, and cholesterol content,** governs membrane packing, fluidity, particle size and phase transition temperature (T_m).
- Our **goal** is to to link lipid composition to sHDL size and T_m and to connect T_m with HDL remodeling efficiency in human plasma.
- Overall, the work aims to guide better sHDL design for atherosclerosis and drug delivery.

2. Methods



3. Results

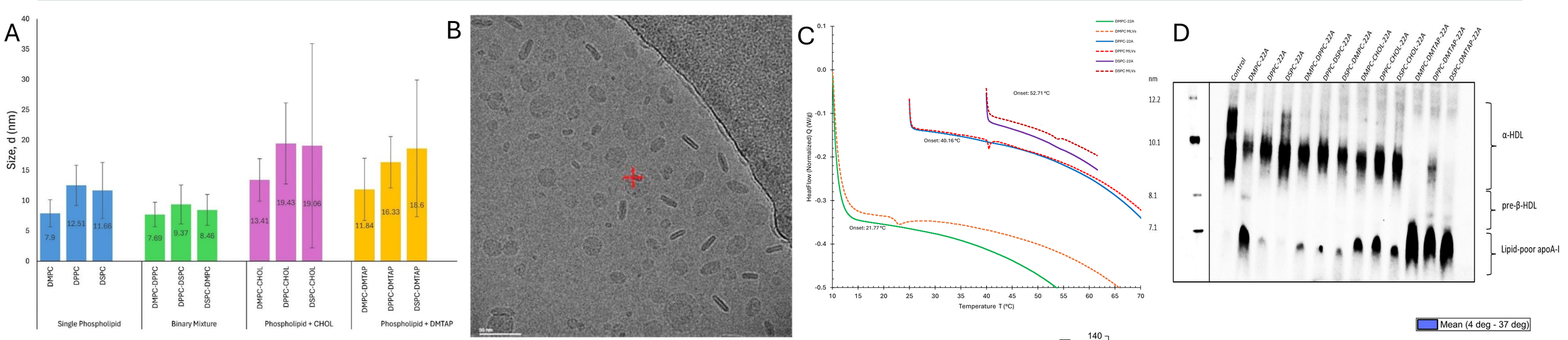


Figure 1: Characterization of sHDL particles. A) Size distribution of different sHDL particles. B) Cryogenic transmission electron microscopy image of DMPC-DMTAP-22A particles. C) Differential scanning calorimetry (DSC) scans of sHDL particles and Liposomes, presented as normalized heat flow Q(W/g) as a function of temperature (°C).

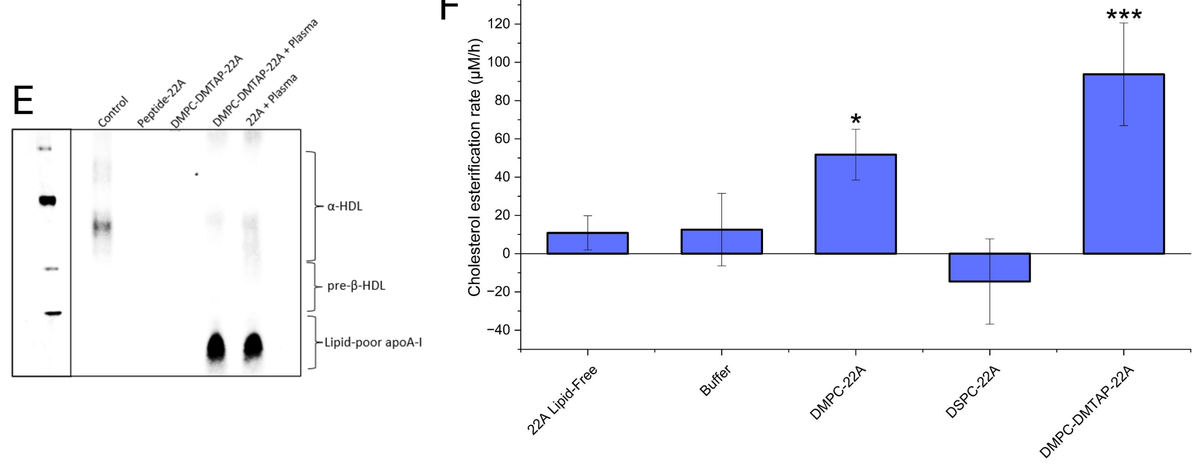


Figure 2: Functional characterization of sHDL particles. D) Remodeling of endogenous HDL in human plasma by s-HDL particles. E) Specificity of the anti-apoA-I antibody F) LCAT activation in human plasma.

4. Conclusions and Perspectives

- **Synthethic HDL remodeling potency and plasma cholesterol esterification are strongly governed by lipid composition**
- **Fine-tuning these properties offers a rational blueprint for developing more effective sHDL formulations to combat atherosclerosis and to develop sHDL-based drug delivery applications**
- **Investigate inter-individual variability in sHDL-induced HDL remodeling and determine whether remodeling efficiency correlates with markers of atheroprotection**
- **Evaluate the relationship between sHDL remodeling potency and atherosclerotic plaque regression in preclinical animal models**

5. References

1. Fawaz M V., Kim SY, Li D, et al (2020) Phospholipid Component Defines Pharmacokinetic and Pharmacodynamic Properties of Synthetic High-Density Lipoproteins. J Pharmacol Exp Ther 372:193–204. https://doi.org/10.1124/JPET.119.257568

2. Yuan W, Ernst K, Kuai R, et al (2023) Systematic evaluation of the effect of different apolipoprotein A-I mimetic peptides on the performance of synthetic high-density lipoproteins in vivo and in vivo. Nanomedicine 48:102646. https://doi.org/10.1016/J.NANO.2022.102646

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