Beyond the Protein Corona - Lipids Matter for Biological Response of Nanocarriers

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In order to use nanomaterials for biomedical applications in a predictable manner (e.g. as systems for targeted drug delivery in the blood stream), their interactions with the different components of the organism need to be understood and controlled. While adsorption processes of different proteins of the human blood onto nanocarrier systems have been investigated thoroughly in the past[1-2], the interactions of lipids and lipid-like molecules in the blood with nanocarriers are still widely unknown. Usually, phospholipids, cholesterol, triglycerides and cholesteryl esters are distributed in the body though the blood stream in the form of lipoprotein clusters with a concentration depending on food intake and physical constitution. These micelle-like lipoproteins are held together by protein components, the so called apolipoproteins. If interaction occurs, the question arises whether the lipoproteins will disintegrate upon contact with the nanomaterial's surface or if complete lipoprotein cluster will interact with the nanoparticles.[3] Following this, we examined interactions of different lipoproteins and their components with polystyrene nanoparticles as model systems for nanocarriers *via* isothermal titration calorimetry (ITC) in order to determine the thermodynamic adsorption parameters of the interaction process and to address the mode and consequences of their interaction.

Our data indicate that lipoproteins will disintegrate upon direct contact with polystyrene nanoparticles and that all components including the hydrophobic molecules adsorb on the surface, while excessive lipoproteins remain intact after surface saturation of the nanoparticles is reached. This can most dominantly be observed in the large change of enthalpy (relative to complete lipoprotein clusters) during interactions between all lipoprotein classes and the nanoparticles *via* ITC. Additionally, this could be imaged by using transmission electron microscopy. As a result of the lipoprotein adsorption, cell uptake into macrophages was significantly reduced, which means that the biological behavior of nanocarriers could be greatly influenced by external factors such as nutrition.

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[1] S. Winzen, et al., Complementary analysis of the hard and soft protein corona: sample preparation critically effects corona composition, *Nanoscale* **2015**, *7*, 2992-3001.

[2] E. Vogler, Protein adsorption in three dimensions, *Biomaterials* **2012**, *33*, 1201-1237.

[3] E. Hellstrand, et al., Complete high-density lipoproteins in nanoparticle corona, *FEBS Journal* **2009**, *276*, 3372 – 3381.