Nanomedicine modifications in biological fluids, interaction with cell receptors and mechanism of uptake

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Understanding at the molecular level of how nanoparticles are processed by cells is crucial to guide the design of nanomedicines with the desired outcomes at the cell level.

We previously showed that the biomolecules adsorbing on nanomedicines upon administration in biological fluids (the biomolecule corona) can interact with specific cell receptors and affect the mechanism cells use for their internalization. By correlating corona composition and cell uptake efficiency, corona proteins promoting or reducing uptake can be discovered. Alternatively, we used reversible biotinylation of cell membrane proteins in live cells to directly identify nanoparticle receptors.

Importantly, we found that even when interacting with specific receptors, nanoparticles can be internalized by cells via different mechanisms than what is usually observed for their endogenous ligands. For instance, nanoparticles interacting with the LDL receptor (LDLR) via their corona are internalized by cells via a mechanism that is not clathrin-mediated. In order to further characterize the mechanism involved, we used a genome-wide forward genetic screening to identify the proteins mediating their internalization and intracellular accumulation. We found that in addition to LDLR, another lipid particle receptor, the scavenger receptor SRB1 also mediates nanoparticle uptake. Additionally, cell surface proteoglycans also act as nanoparticle receptors and, opposite to what is often believed, they mediate specific interactions that do not depend simply on charge but vary depending on cell type and nanoparticle properties.

Our findings highlight the importance of understanding how cells interact with and process nano-sized materials in order to improve nanomedicine design.