The Miracle of PEGylation: Specific Proteins Determine the Stealth Effect of Polyethylene Glycol

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Abstract

PEGylation is today's gold standard for drug delivery vehicles to reduce unspecific cell uptake, i.e. to establish a "stealth" effect. As it is thought that the reduction of protein absorption is the critical parameter for the stealth effect while still a detectable amount is present we chose to combine the critical techniques. Three intriguing findings are reported:[1] First, both PEG- and – and also interestingly PEEP-modified nanocarriers - are not internalized by cells and exhibit a reduced protein adsorption after incubation with human plasma. Secondly and more intriguingly, all particles are strongly internalized by cells if not previously incubated with human plasma. Third and most importantly, we have shown by quantitative proteomic mass spectrometry of the protein corona on both stealth nanoparticles that clusterin – also known as apolipoprotein J (ApoJ) is the major component in both protein mixtures and that plasma as well as clusterin alone act as "cell-repellents". This established the necessity of distinct plasma proteins at the nanocarriers' surface to mediate the stealth effect.
Furthermore we investigated different sources of protein (serum versus plasma, human versus bovine) and showed specific effects on cellular uptake depending on the type of protein source used.[2] At this point citrate plasma seems to be an ideal source for in vitro experiments.
Even uptake[3] and intracellular trafficking[4] of nanoparticles can be followed by using the specific proteins attaching or surrounding the nanocarriers.

[1] Nature nanotechnology (2016) 11, 372-377
[2] Nanoscale (2016) 8, 5526-5536
[3] Biomacromolecules (2015) 16, 1311-1321
[4] ACS Nano (2014) 8, 10077-10088