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Major role of complement activation compared to protein corona composition in the capture of stealth-NP by phagocytes: Inter-individual and inter-species variability

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Understanding the functional properties of a new nano-biointerface created by host proteins adsorbed on nanoparticles (NPs), or nanoparticle protein corona, masking the pristine nanomaterial is considered by many the obliged “golden gate” to their clinical application. Rapid clearance by the reticular endothelial system (RES) phagocytes is a major obstacles for nanotheranostics developments and the protein corona may indeed favor or hamper such process. However, also complement activation may increase RES clearance and contribute to proinflammatory and infusion-related reactions. Poly(ethylene glycol) (PEG) NPs coatings, used to minimize protein interaction and RES clearance (stealth effect) may trigger complement, thereby improving phagocytes capture and infusion-related reactions. Poly(2-methyl-2-oxazoline) (PMOXA) and poly(2-ethyl-2-oxazoline) (PETOXA) have been proposed as alternative polymer for NP surface modification, due to their improved chemical/physicochemical features compared with PEG. We characterized PEG, PMOXA and PETOXA performance and evaluated the relative importance of protein corona formation vs complement activation. Specifically, we tested the efficacy of human monocytes, macrophages and PMNGs to capture 100 nm ORMOSIL-NPs, coated with above indicated polymers, in human serum. PEG and, especially, PMOXA and PETOXA coatings increased complement activation and opsonine-mediated NP capture by phagocytes compared to naked NPs. The surface-dependent composition diversities of the serum protein corona formed on the different NP formulations were poorly relevant since, in the absence of complement, a similar stealth effect was invariably measured. Tests using sera from different human subjects, mice and pigs showed crucial subject- and species-dependent differences. We conclude that complement cascade activation is a major factor negatively affecting the stealthing efficacy of PEG, PMOXA and PETOXA coats on NPs. Species-specific diversities of such mechanisms in pre-clinical models, e.g. the murine one, may lead to wrong NP efficacy extrapolations to the human contest. This demands the search for complement-inert nanoparticle coatings.

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