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On The Importance of Understanding Biointeractions of Nanomaterials with the Immune System

Editorial

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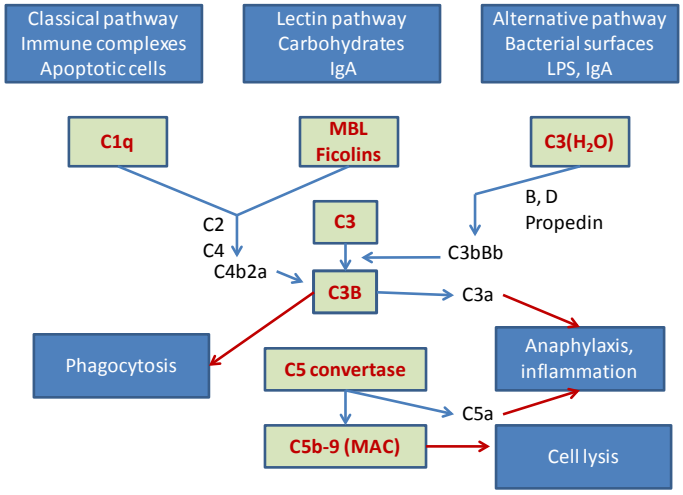
In this brief editorial we would like to express our opinion on one of the most urgent problems in the field of nanomedicine. A recent review by Weissleder and colleagues [1] nicely summarized this problem in the following paragraph: "Reviewing recent literature reveals a disequilibrium: an exponentially growing number of papers describe the synthesis of new nanomaterials, but relatively few manuscripts comprehensively investigate the biological behavior and/or advantages over existing materials. We clearly need more of the latter. Indeed, an argument could be made that all new nanomaterials should be accompanied by more comprehensive biological profiling, including cytometry analysis of cell distribution and other biological assays".

The same opinion was voiced by other leading experts in the field of nanomedicine [2, 3]. It is definitely important to engineer and manufacture newnanomaterials with novel characteristics, precise physicochemical properties and accurate drug loading. However, we are convinced that basic research aimed at understanding the biological behavior of nanocarriers, such as interactions with immune proteins and extra- and intracellular immune receptors is critically important and is desperately needed in order to move the filed of nanomedicine forward.

One of the best examples of the existing disequilibrium is the role of the complement system (CS) in nanoparticle toxicity and clearance. CS accounts for about 5% of globulins in serum and is responsible for recognition, elimination and destruction of pathogens (Fig. 1). Activation of the CS triggers the release of C3a and C5a,which are the most potent known proinflammatory molecules and anaphylatoxins. Opsonization of pathogen surface with C3b and C1q can cause recognition and clearance by macrophages[4]. Many nanoparticulate systems have been shown to trigger the CS activation, [5-15] and it is doubtless that the ones that have not been tested in the relevant assays also do so, simply due to the fact that they "foreign" to the body. The importance of the CS is exemplified by the fact that several generations of dextran iron oxide nanoparticles for magnetic resonance imaging (Feridex, Combidex, Resovist) have been withdrawn from the market because of widespread infusion-related side effects due to the CS activation. At the same time, despite the critical role of the CS, the mechanisms of the CS activation by nanomedicines are still poorly understood and have not been fully investigated. Thus, as of the date of writing this editorial, there are approximately 87,000 "nanoparticle" hits in PubMed. If we do the search using the "complement" keyword, there are 143,000 hits in the PubMed. If we combine "nanoparticle AND complement" in the search, there are only 263 hits. So, out of all the papers that deal with nanoparticles, only 0.3% of these papers (or less) somehow relate to the complement aspect. The same disequilibrium is notable in the research funding: the search of the NIH funding portfolio (http://projectreporter.nih.gov) revealed that while there are 65 projects that contain "nanoparticle AND complement" keyword, none of them specifically deals with mechanisms of complement activation of nanoparticles and strategies to prevent the phenomenon through chemistry/rational design.

Also underrepresented in the existing research portfolio are the mechanisms of recognition of nanoparticles by macrophages, which are arguably the most important cells responsible for rapid clearance of nanomedicines, the most undesirable and frustrating phenomenon in the nanomedicine field. The current strategy to avoid nanoparticle immune clearance is using the set of old generic rules on decorating the surface of nanoparticles with polymers. This coating has been shown to create a brush border around nanoparticles and is postulated to provide non-specific impermeable barrier that sterically prevents access of plasma proteins and cell receptors and thereby promotes long circulation time of nanoparticles [16, 17]. The best example is long-chain polyethylene glycol (PEG), albeit other hydrophilic polymers such as Pluronic F68 [18-20], Poloxamer (block copolymer of polyethylene oxide and polypropylene oxide [21]) and polyvinylpyrrolidone [22] have been used. The surface grafting with PEG has been widely employed with many types of nanoparticles and is being used in commercial liposomal doxorubicin formulation Doxil™. As a rule, increasing polymer thickness and density decreases the macrophage recognition and prolongs the circulation time [16-23]. However, polymer coated nanoparticles are still recognizable

Figure 1: Simberg and Tsigelny



by liver and spleen macrophages (over 60-80% of the injected dose) and trigger complement activation. Another important shortcoming of the PEGylation is the apparent decrease in the affinity of surface tethered ligands due to the interference of the surrounding brush layer [24]. Small molecule (peptide)-mediated targeting should be especially sensitive due to ahigher chance of being buried and masked in the PEG brush layer. Another intrinsic limitation of PEGylation is the masking of nanoparticle's surface, mitigating potentially attractive properties of nanoparticles such as enzyme binding and activation, absorption of specific biomarkers, or change in optical properties.

We think it is high time for the nanomedicine field to take a step back and delve into the basic immunological aspects of interactions of all new and old nanomaterials with the biological milieu. This approach could be potentially rewarding as it could lead to important discoveries in order to advance the field that is still stuck in "PEG" paradigm[25]. The knowledge of how nanoparticles are recognized by immune proteins and receptors could be used for more efficient "camouflaging" of the nanoparticle surface, as compared to the empirical polymer coating. As a consequence, the increased circulation time can allow reducing the injected dose and achieving less deposition in the immune organs and more focal imaging/therapy compared with non-optimized nanoparticles.We predict that mechanistic studies of the bio-nano interface will enable nano-engineers and nano-chemists to perform rational (*in silico?*) design of nanoparticles with improved safety and efficacy.

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