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Cover Story

Impact of anti-PEG antibodies on PEGylated nanoparticles fate *in vivo*

In the early 1990s, the groups of Teresa Allen [1] and Robert Langer [2] have published seminal papers demonstrating that coating liposomes and polymeric nanoparticles with poly(ethylene glycol) (PEG) could significantly enhance their residence time in the bloodstream. The flexible and hydrophilic nature of the polymer prevents the adsorption of opsonins to the surface of nanomaterials and delays uptake by the mononuclear phagocyte system. Since then, PEG has become the gold standard to confer long circulation to nanomaterials used in drug delivery and imaging applications.

Despite the recognized benefits of PEGylation, however, subsequent studies have shown that the polymer is not without shortcomings and is more immunogenic than initially thought. The studies published in early 2000s showed that repeated injection to animals significantly increased clearance between the first and second doses of PEGylated liposomes [3,4]. This occurrence, called the "accelerated blood clearance (ABC) phenomenon", was attributed to the development of anti-PEG antibodies [5]. In parallel, multiple clinical studies have shown that 40-72% of healthy patients could have detectable levels of anti-PEG antibodies in their blood, even without prior exposure to PEG-containing drugs [6,7]. This phenotype cannot be overlooked for the translational development of PEGylated nanomedicines.

In the current issue, Professor Nicolas Bertrand and his colleagues show that anti-PEG antibodies modify the nature of the proteins which adsorb on the surface of nanoparticles [8]. They postulate that this altered protein corona can explain the accelerated clearance, notably by changing the mechanisms governing the removal of nanoparticles from the bloodstream. The Bertrand team used a model where an immune response was induced by injecting long-circulating polymer nanoparticles to immunocompetent mice to understand what happens upon re-exposure to nanomedicines. They compared the pharmacokinetics of various nanosystems in the presence and absence of circulating anti-PEG antibodies. They showed that, although the antibodies could alter the circulation of PEGylated polymeric and liposomal nanoparticles, the pharmacokinetics of free polymer and PEGylated bovine serum albumin remained unchanged. They observed that the *in vitro* binding of anti-PEG IgM to nanoparticles was higher compared with PEGylated proteins, presumably due to the regular orientation of polymer chains on the surface. This facilitated binding of anti-PEG IgM triggered the activation of the complement system by nanoparticles, while the immune cascade remained unaffected by the incubation of PEGylated albumin in plasma containing anti-PEG antibodies. Finally, the Bertrand team highlighted that the accelerated clearance due to anti-PEG IgMs could be partially mitigated by blocking the activation of the complement cascade *in vivo*.

The study by the Bertrand team is important for a number of reasons. It provides a systematic understanding of the ABC phenomenon, advancing our understanding of the fate of PEGylated nanomedicines in patients with pre-existing anti-PEG antibodies. The team focused their work on IgMs, an isotype of immunoglobulins which is produced during early immune responses. Although this subclass represents about half of anti-PEG antibodies observed in patients, further work is required to assess whether IgGs, which are also observed clinically, function in the same manner. Should these studies confirm the importance of the cascade, *in vitro* complement activation could become a useful way of screening the susceptibility of various new materials to the accelerated blood clearance effect or predicting which patients are more susceptible to experience the phenomenon. Furthermore, the study suggests that the environmental and epidemiological considerations leading to the development of anti-PEG antibodies could influence the therapeutic efficacy of some clinically used PEGylated formulations. If future studies confirm that patients are developing anti-PEG immune responses over the years, the efficacy of some PEGylated therapeutics might have to be re-evaluated, even after showing efficacy at the time of clinical studies. The drug delivery field moves forward with studies like that of the Bertrand team, focusing on the mechanistic understanding of the ABC phenomenon and providing invaluable information for development of PEGylated formulations.

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