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Anti-polyethylene glycol antibodies alter the protein corona deposited on nanoparticles and the physiological pathways regulating their fate *in vivo*

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Abstract

Multiple studies highlight the strong prevalence of anti-poly(ethylene glycol) (anti-PEG) antibodies in the general human population. As we develop therapeutic modalities using this polymer, it is increasingly relevant to assess the importance of anti-PEG antibodies on biological performances. Here, we show that the anti-PEG Immunoglobulin M (IgM) raised in mice following the injection of polymeric nanoparticles could have significant neutralizing effects on subsequent doses of PEGylated nanosystems *in vivo*. The circulation times of PEGylated nanoparticles and liposomes were strongly reduced in animals with circulating anti-PEG IgMs, irrespective of the PEG density or the surface properties of the system. In comparison, despite that anti-PEG IgMs could bind free methoxy-terminated PEG and PEGylated bovine serum albumin, the circulation kinetics of these systems remained unaltered in the presence of antibodies. The binding of IgMs to the PEGylated surface of nanoparticles alters the nature of the proteins adsorbed in the surrounding corona, notably due to the activation of the complement cascade. These changes are responsible for the observed differences in circulation times. In comparison, the PEG-BSA is unable to activate complement, even in the presence of anti-PEG IgMs. These results inform on how anti-PEG antibodies can affect the fate of PEGylated nanomaterials and highlight how the architecture of nanoparticles impacts the deposition of the protein corona.

Keywords Anti-drug antibodies (ADA), poly(ethylene glycol)-b-poly(lactic co glycolic acid) (PEG-PLGA), nanoparticles, drug delivery, pharmacokinetics, biodistribution, liposomes.

1. Introduction

Upon entering the bloodstream and other physiological environments, the surface of nanomaterials absorbs a complex corona of proteins that influences how they are subsequently perceived by biological systems [1, 2]. Understanding which proteins are involved in this corona and how they can alter the interactions of nanomaterials with living systems is an important prerogative to design more effective nanoparticles for biomedical applications [3]. Various sophisticated studies have described how the deposition of proteins on nanoparticles can affect *in vitro* interactions with macrophages [4, 5] or cancer cells [6]. Nevertheless, understanding how the protein corona affects the fate of nanoparticles in living organisms with functional circulatory, metabolic and immune systems is of paramount importance for the development of safe and effective nanomedicines.

In addition to model polystyrene or inorganic nanoparticles that can inform on fundamental concepts [5, 6], mechanistic studies must also include materials which are used clinically or are being developed for translational applications. In general, these materials need to be engineered to limit