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Impact of anti-PEG antibodies induced by SARS-CoV-2 mRNA vaccines

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The successful mRNA vaccines against COVID-19 contain polyethylene glycol (PEG) to stabilize the lipid nanoparticles. Recent data show that PEG-specific antibodies can be induced or boosted by mRNA vaccination. Further research is needed to study the potential links between PEG-specific antibodies, vaccine reactogenicity and enhanced clearance of other PEG-containing medicines.

Polyethylene glycol (PEG) is a non-toxic, hydrophilic polymer with a broad range of applications in cosmetics, personal care products and pharmaceutical formulations. PEGylation is widely used in bioconjugation and nanomedicine to maintain colloidal stability of nanoparticles and to reduce the clearance of nanomedicines in vivo, improving delivery efficiency and safety. However, under certain circumstances, PEG is weakly immunogenic, and a proportion of humans have developed low levels of PEG-specific antibodies. Such antibodies can lead to enhanced clearance of systemically delivered PEGylated nanomedicines and limit their efficacy[1].

mRNA vaccines and other therapeutics incorporate PEG into the lipidic components of the lipid nanoparticle (LNP) to stabilize the particles. Four recent studies found that SARS-CoV-2 LNP-based mRNA (mRNA–LNP) vaccines can induce or boost anti-PEG antibodies in humans[2–5]. However, the clinical impact of elevated levels of anti-PEG antibodies is still unclear. Furthermore, a mechanistic understanding of how anti-PEG antibodies are induced in humans is lacking.

More research is needed to understand PEG immunogenicity in mRNA vaccines and how this might impact the development of the next-generation of vaccines (Fig. 1). A key question is why does the Moderna mRNA-1273 vaccine have greater PEG immunogenicity than the Pfizer BNT162b2 vaccine[2,3]? Is this due to a dose-dependent effect or other factors? The key factors that modulate PEG immunogenicity of mRNA–LNP vaccines are largely unknown. Individual factors (such as genetics, lifestyle and underlying health conditions) may also influence mRNA vaccine immunogenicity and reactogenicity. For example, we and others observed that pre-existing levels of anti-PEG antibodies vary widely among healthy adults and are more common in younger females[2,6].

Potential impact of anti-PEG antibodies

Estimates of the seroprevalence of anti-PEG antibodies in healthy individuals vary widely, which is likely influenced by the population studied and the sensitivity of the assay used[1]. In agreement with previous reports, we found pre-existing anti-PEG antibodies at variable levels (ranging in enzyme-linked immunosorbent assay (ELISA) end point titre from 1:12 to 1:3,000) in plasma from 71% of subjects prior to mRNA vaccination[2]. Anti-PEG IgG levels increased a mean of 13–17 fold after the second 100 µg dose of the mRNA-1273 vaccine but to a much lesser extent after the second 30 µg dose of the BNT162b2 vaccine (1.1–1.8 fold)[2,3].

mRNA vaccines are reactogenic, commonly leading to considerable injection site effects and systemic effects, such as fever, myalgia or headache. Higher reactogenicity of mRNA-1273 versus BNT162b2 is observed but the cause of these differences is unclear[7]. Possible factors include a higher dose of mRNA in the mRNA-1273 formulation and/or differences in the LNP composition. One of our studies showed a correlation between anti-PEG IgG antibody levels and increased systemic vaccine reactogenicity following two vaccine doses[2]. Given that the booster doses of SARS-CoV-2 mRNA–LNP vaccines may further increase the levels of PEG-specific antibodies, it is important to validate this potential association with larger clinical studies.

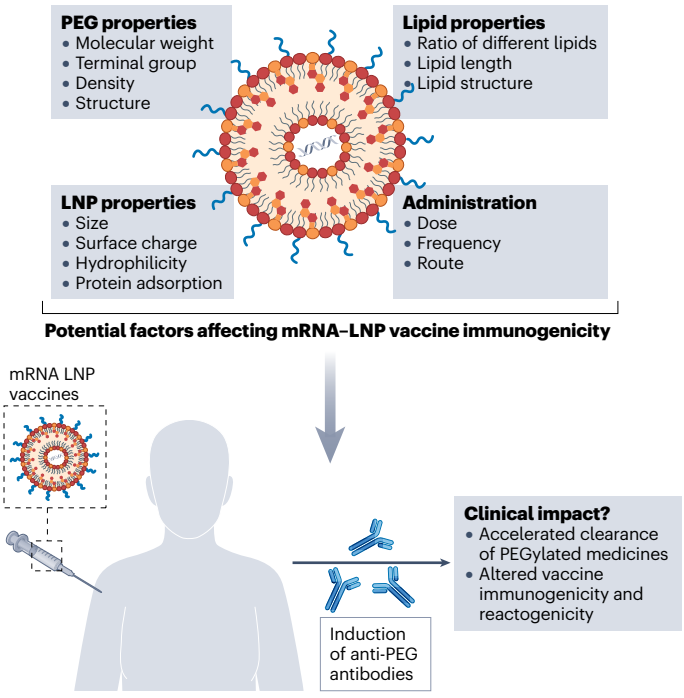

Fig. 1 | Induction of anti-PEG antibodies by mRNA vaccines. Anti-polyethylene glycol (PEG) antibodies can be induced by mRNA–LNP vaccines, but the mechanisms involved and clinical impact of these antibodies are still unknown. The upper panel highlights potential factors that may influence PEG immunogenicity, whereas the lower panel summarises the potential clinical impact of anti-PEG antibodies induced by mRNA–LNP vaccines.

Our studies to date[2] have not shown any impact of anti-PEG antibodies on the SARS-CoV-2 neutralizing antibody response after two doses of mRNA-1273, but it will be important to monitor this after additional booster doses. Guerrini et al. also found that the presence of anti-PEG antibodies did not influence the level of anti-spike antibodies generated by vaccination[4]. As mRNA vaccines traverse lymphatics to reach draining lymph nodes, opsonization of mRNA–LNP with PEG antibodies may not limit vaccine expression and immunogenicity. Nonetheless, larger long-term clinical studies, supported by incisive animal studies, using multiple booster mRNA vaccines are needed to assess whether anti-PEG antibodies may ultimately limit vaccine effectiveness.

It has been extensively shown that anti-PEG antibodies can induce faster clearance of systemically delivered PEGylated drugs, including therapies used to treat patients with cancer, gout or genetic diseases. Anti-PEG antibodies induce the formation of nanoparticle–antibody immune complexes, which promote complement activation and phagocytosis[1]. In one of our studies, we observed that the rise in PEG-specific antibodies following mRNA-1273 vaccination correlated with a significant increase in the uptake of PEGylated nanomaterials by blood phagocytes ex vivo[2]. The PEG-specific antibodies induced by mRNA-1273 vaccination were also able to fix complement in direct proportion to their levels[2]. This suggests that elevated levels of anti-PEG antibodies may promote sequestration of PEG-containing nanomedicines through complement opsonization, which may lead to accelerated blood clearance. However, further studies are needed to understand whether anti-PEG antibodies induced by mRNA–LNP administration can promote accelerated clearance of other nanomedicines.

Can we overcome PEG immunogenicity?

A key first step will be to standardize the measurement of anti-PEG antibodies. Current assays are commonly in house ELISAs and likely have widely varying sensitivity and specificity. There is a need for an international set of standards, such as a set of plasma samples containing a wide range of anti-PEG antibodies to standardize results across laboratories. The use of positive controls, such as panels of monoclonal antibodies against different PEG epitopes, will also help standardize measurements[6]. This is urgently needed as the field matures.

Understanding the induction of anti-PEG antibodies will be important for designing the next generation of mRNA–LNP vaccines. For example, the induction of anti-PEG antibodies in mice was reported to depend on the rate at which PEGylated lipid was shed from LNPs, with fast shedding inducing less anti-PEG antibodies[8]. Likewise, the terminal group of PEG was found to influence PEG immunogenicity, with hydroxy-PEG being less immunogenic than methoxy-PEG[9]. Alternative polymers that mimic the stealth properties of PEG, including zwitterionic and hydrophilic polymers, are in development[10]. Future studies will focus on developing mRNA–LNPs stabilized with PEG alternatives and evaluating their potential for clinical translation.

Conclusions

The rapid development of SARS-CoV-2 mRNA–LNP vaccines saved many lives and they are generally safe. mRNA–LNP vaccines use PEGylated nanomaterials and recent reports have shown they can induce anti-PEG antibodies in vaccinated individuals. The overall impact of boosting anti-PEG antibodies by mRNA-LNP vaccines is not yet clear, but given the repeated delivery of SARS-CoV-2 mRNA vaccines to large human populations and the rapid development of other PEGylated nanomedicines, this topic requires further study.

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Competing interests

The authors declare no competing interests.