IgM responses following SARS-CoV-2 vaccination: insights into protective and pre-existing immunity

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Antigen-specific antibody responses are monitored as measures of protective immunity following anti-SARS-CoV-2 vaccination. Immunoglobulin (Ig)M antibodies are produced early in the humoral immune response against viral infections and provide fast protective immunity. Next, following maturation and isotype class-switching, memory IgG antibodies with increased affinity are produced. The current mRNA vaccines against SARS-CoV-2 induce robust IgG responses that have been the subject of intensive investigation.[1–3] However, vaccine-induced IgM responses are less well characterised in terms of timing and the role of pre-existing immunity. The importance of IgM in protective immunity against COVID-19 was emphasized by the strong association between declining neutralizing antibody responses and declining anti-spike (S) protein and anti-receptor binding domain (RBD) IgM levels.[4,5] In this article of *eBioMedicine*, Ruggiero et al. performed a longitudinal study of a large cohort of health care workers to study the dynamic IgM response following BNT162b2 vaccination in naÿve and previously infected individuals with SARS-CoV-2.[6] This is an interesting and timely study that sheds more light on the crucial role of IgM in the development of protective immunity and on pre-existing and novel humoral immunity to SARS-CoV-2.

In this study, anti-S IgM and IgG levels were longitudinally measured in a large cohort of 1,873 health care workers receiving the BNT162b2 vaccine, including 1,584 immunologically naÿve to SARS-CoV-2 and 289 with a history of previous infection. Samples were collected before vaccination, at the second vaccine dose and three weeks after the second vaccine dose. The authors describe three patterns of anti-S IgG and IgM responses in naive vaccinees: (i) absence of IgM, (ii) development of IgM following IgG appearance and (iii) simultaneous presence of IgM and IgG. This latter coordinated IgM and IgG response was associated with higher virus-neutralizing activity, which suggests that anti-S IgM antibodies may contribute to protective immunity. In addition, the first two groups of vaccinated health care workers presenting with unconventional IgM responses, namely no IgM response or IgM appearing after IgG, showed significantly lower anti-S IgG levels compared to those with a coordinated humoral response to the vaccine. This indicates that a coordinated humoral response with both anti-S IgM and IgG antibodies is associated with increased protective immunity. The absence of anti-S IgM following vaccination could point towards pre-existing immunity to cross-reactive human coronaviruses. In this regard, the anti-SARS-CoV-2 IgG response was shown to be more cross-reactive across a range of human coronaviruses while the specific IgM response was highly specific.[7]

In vaccinees with a history of previous SARS-CoV-2 infection, again three patterns of anti-S IgM responses were described: (i) absence of IgM, (ii) persistent IgM response before and after vaccination and (iii) "delayed" IgM response that appeared after vaccination. The absence of anti-S IgM antibodies corresponds to the expected decay of a previous primary immune response against the virus. The persistence of virus-specific IgM responses could refer to the persistence of non class-switched IgM^+ memory B cells.[8] The induction of anti-S IgM after vaccination in health care workers with a history of previous infection is unexpected but could point towards the inability of these subjects to mount an efficient antibody response, possibly due to a transient or asymptomatic previous infection.[9] Therefore, these subjects could respond to the vaccination with an IgM and IgG response resembling that of a primary immune response.

The merits of this study include the longitudinal analysis of a large cohort of subjects that allowed the discrimination between subjects naÿve to SARS-CoV-2 and subjects with a previous SARS-CoV-2 infection. Furthermore, clinically validated assays were used for the analysis of anti-S IgM and IgG levels although the sensitivity of these assays, with a positive predicted value (PPV) for the IgM assay of 92.07%, could be a point of discussion as also indicated by the authors. A more elaborate evaluation of the antibody response including other Ig isotypes (e.g. IgG1, IgG2, IgA) could provide more information on the class-switching response in those individuals with a history of previous SARS-CoV-2 infection who displayed a "delayed" anti-S IgM response. Furthermore, future studies should combine

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the analysis of IgM, IgG and IgA responses with cellular immune responses (B cells, $CD4^+$ T cells, $CD8^+$ T cells) in natural infection and vaccination to study the dynamic aspects of the combined adaptive immune response. Such analyses previously indicated that coordinated responses confer protective immunity in contrast to uncoordinated responses, with a connection between aging and impaired adaptive anti-SARS-CoV-2 immune responses.[10] In addition, the observed dynamic anti-S IgM responses should be correlated with vaccine efficacy to obtain more insight into the role of vaccine-specific IgM responses in the induction of protective immunity. In this way, detailed monitoring of vaccine-specific adaptive immune responses can be used as a measure of protective immunity to SARS-CoV-2 infection. This is important to guide vaccination plans and public health decisions.

Declaration of interests

The author declares no conflicts of interest.

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