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Strategies to Prevent SARS-CoV-2-Mediated Eosinophilic Disease in Association with COVID-19 Vaccination and Infection

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Abstract
A vaccine to protect against COVID-19 is urgently needed. Such a vaccine should efficiently induce high-affinity neutralizing antibodies which neutralize SARS-CoV-2, the cause of COVID-19. However, there is a concern regarding both vaccine-induced eosinophilic lung disease and eosinophil-associated Th2 immunopotentiation following infection after vaccination. Here, we review the anticipated characteristics of a COVID-19 vaccine to avoid vaccine-associated eosinophil immunopathology.

Introduction

COVID-19 is a new infectious disease caused by a coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The virus exhibits high infectivity and can cause a broad spectrum of symptoms and severity [2]. To limit the damage of COVID-19, primary efforts focus on confinement, with physical distancing, wearing face masks, and hygiene measures [3]. However, although these measures help against viral spread, they cause limitations in our personal and professional lives. Moreover, there is a constant risk of viral outbreaks with severe consequences for health and economics. Therefore, rapid immunization of the world's population against SARS- CoV-2 is needed and vaccines are currently being developed world-wide [4]. There are several strategies to develop a vaccine such as live-attenuated or inactivated viruses, viral vector-containing nanoparticles or virus-like particles, subunit components, proteins/peptides, RNA, DNA, or even viable cells. These strategies are reviewed elsewhere [4]. In this article, we would like to point out the risk of eosinophil-associated immunopathology following infection after SARS-CoV-2 vaccination as well as strategies for its prevention.

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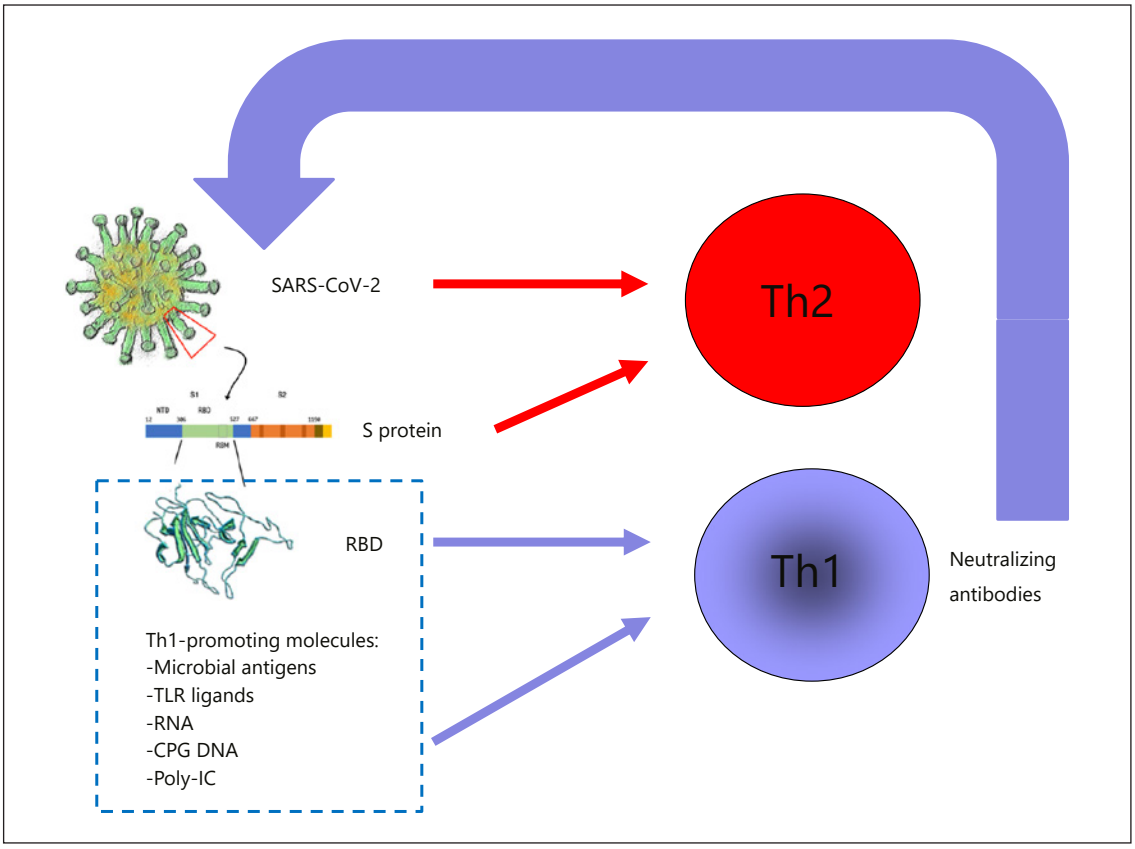

Fig. 1. An illustrated presentation of the anticipated type 1 and type 2 immune responses by SARS-CoV-2, the spike (S) protein and its receptor binding domain (RBD). Based on information about SARS-CoV-1, the whole virus and the complete S protein induce type 2 immune responses. In contrast, RBD does not induce type 2 inflammation. It is suggested that a COVID-19 vaccine should contain the RBD and additional Th1-promoting molecules (dashed box). High-affinity SARS-CoV-2 neutralizing antibodies are the best protection against virus-induced type 2 eosinophilic inflammation upon re-challenge.

COVID-19 and Eosinophils

Eosinophils represent a subpopulation of granulocytes which can mediate immunopathology in eosinophilic diseases such as bronchial asthma, eosinophilic esophagitis, and hypereosinophilic syndromes [5]. Eosinophils are believed to exhibit antibacterial and antiviral effector functions as well as protecting against parasites [6, 7]. Although rhinovirus, respiratory syncytial virus (RSV), and influenza virus are common triggers of viral-induced asthma exacerbation, neither SARS-CoV-1 nor SARS-CoV-2 have been identified as risk factors for asthma exacerbations [8, 9]. Interestingly, COVID-19 patients exhibited eosinopenia while eosinophil levels increased in association with improved clinical status [9]. Moreover, in a patient with COVID-19, a lymphocytic infiltration of the lungs was observed, whereas no eosinophil infiltration was detected [10]. Taken together, although the available data are very limited, eosinophils do not seem to play either a protective or pathogenic role in COVID-19 under normal circumstances.

But how about the role of eosinophils during coronavirus vaccination? SARS-CoV-1 vaccines have been shown to induce pulmonary eosinophilia in ferrets [11], monkeys [11], and mice [12] after viral challenge. Eosinophil-associated type 2 inflammation also occurred with SARS-CoV-1 reinfection in monkeys [13]. Eosinophil-associated pulmonary disease was also seen subsequent to infection after RSV vaccination [14]. Therefore, there is the possibility that SARS-CoV-2 vaccines might cause a similar vaccine-associated immunopathology.

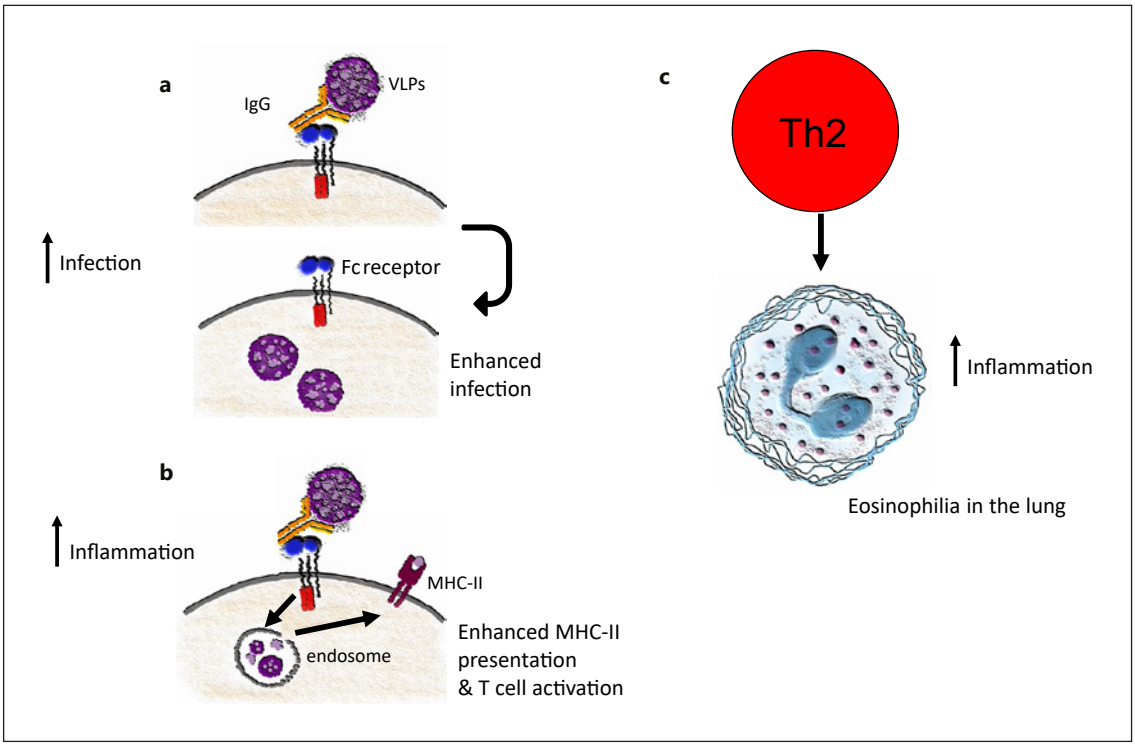

Fig. 2. Vaccination may enhance disease by induction of IgG antibodies (left) or Th2 cells (right). **a** IgG antibodies may enhance infection if the cellular target of infection expresses Fcγ receptors. **b** Alternatively, IgG antibodies may enhance antigen presentation by targeting viral particles to professional antigen-presenting cells, enhancing inflammation. **c** Th2 cells may recruit eosinophils to the lung, also causing enhanced infection. As SARS-CoV-2 does not infect Fcγ receptor-expressing cells and viral load is expected to be reduced in vaccinated individuals, IgG antibodies are not expected to cause enhanced disease, in particular not neutralizing antibodies. Th2 cell-induced eosinophilia, may, however, be a major concern, and therefore induction of Th2 cells by vaccination should be avoided.

Immune Responses in Association with Coronavirus Vaccination

The most promising strategy for reaching immunity against COVID-19 is to induce the production of virus-neutralizing antibodies (Fig. 1). Such antibodies usually block the interaction of the virus with its cellular receptor. The cellular receptor of SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2) [15]. Therefore, the primary immune mechanism for avoiding infection seems to be by blocking viral attachment to ACE2. Indeed, most COVID-19 vaccine candidates follow this strategy [16]. The obvious isotype to be induced is IgG, particularly the protective IgG1 and IgG3 subclasses. However, since the virus targets mucosal surfaces, IgA induction might also be beneficial. The formulation of the vaccine candidate with Toll-like receptor (TLR) 7/8 and TLR9 ligands to the vaccine might promote IgA production [17, 18] and, in addition, may favor type 1 immune responses (Fig. 1) [19].

To obtain specific antibody production, B cells require "help" from $CD4^+$ T cells. The induction of $CD4^+$ T-helper cells is often not rate limiting in vaccination, most likely because low numbers of these cells are already sufficient for antibody production. Nevertheless, low responders to vaccination often fail to mount IgG responses due to insufficient $CD4^+$ T-cell "help". Since T-cell help can be provided by $CD4^+$ T cells with other antigen specificities, vaccines can be supplemented with microbial proteins or peptides to which most humans are already immunized [20]. The immune response to these antigens will be strong because boosting of previously primed and established $CD4^+$ T cells is more efficient than priming. Such microbial antigens may also skew the immune response towards T-helper type 1 polarization (Fig. 1) [19].

A type 1 immune response might also be attained by viral vectors or innate stimulators with type 1 polarization capabilities [21–23]. For instance, nanoparticles and virus-like particles can be designed to contain molecules that stimulate innate immunity to enhance T-helper 1 and to block T-helper 2 polarization [24].

The type of T-helper immune response may also depend on the antigen. Immunization with inactivated SARS-CoV-1 causes eosinophilic infiltration following viral re-exposure in mice [25]. Immunization with the whole spike (S) protein, which is responsible for binding to ACE2, also triggered type 2 inflammation including eosinophilia after viral challenge in mice [11]. In contrast, at least in the case of SARS-CoV-1, immunization with the so-called receptor binding domain, which is a particular part within the S protein, induced neutralizing antibodies in the absence of a type 2 immune response (Fig. 1) [26].

Increased immune pathology may also occur via antibodies induced by the vaccine (Fig. 2). For example, an antibody enhancement of infection may occur when antibodies promote viral uptake via Fc receptors. However, there is no evidence that such a mechanism occurs with SARS-CoV-1 [27]. On the other hand, antibodies may also activate immunoreceptor tyrosine-based activation motifs within the cytoplasmic domain of Fc receptors, resulting in increased secretion of pro-inflammatory cytokines by macrophages and dendritic cells. Such a scenario, however, requires a high viral load which is unlikely to occur if vaccine-induced neutralizing antibodies are present. Therefore, antibody-dependent enhancement is not expected to cause problems for COVID-19, but eosinophil-mediated immunopathology following SARS-CoV-2 vaccination and infection may be at the heart of the problem (Fig. 2).

Taken together, COVID-19 vaccines should induce high-affinity neutralizing antibodies. Moreover, they should polarize the T-cell response towards type 1 immunity and avoid the stimulation of cytokines which induce T-helper 2 immunity. To avoid type 2 inflammatory responses, careful selection of the vector and the antigen is required. The addition of TLR ligands and other molecules stimulating type 1 immunity might be helpful with respect to sufficient $CD4^+$ T-cell help for antibody production as well as suppressing unwanted type 2 immunity-causing eosinophilia. It should be noted, however, that it is only partially possible to predict vaccine efficacy and safety [28]. Due to its urgency, COVID-19 vaccination should be given the highest priority.

Disclosure Statement

M.F.B. owns shares in Saiba GmbH which is involved in the development of a vaccine against COVID-19. H.-U.S. and A.V.K. declare no conflicts of interest.

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