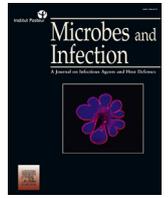




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Commentary

The potential role of Th17 immune responses in coronavirus immunopathology and vaccine-induced immune enhancement

A B S T R A C T

Increasing evidence points to host Th17 inflammatory responses as contributing to the severe lung pathology and mortality of lower respiratory tract infections from coronaviruses. This includes host inflammatory and cytokine responses to COVID-19 caused by the SARS-2 coronavirus (SARS CoV2). From studies conducted in laboratory animals, there are additional concerns about immune enhancement and the role of potential host immunopathology resulting from experimental human COVID-19 vaccines. Here we summarize evidence suggesting there may be partial overlap between the underlying immunopathologic processes linked to both coronavirus infection and vaccination, and a role for Th17 in immune enhancement and eosinophilic pulmonary immunopathology. Such findings help explain the link between viral-vectored coronavirus vaccines and immune enhancement and its reduction through alum adjuvants. Additional research may also clarify links between COVID-19 pulmonary immunopathology and heart disease.

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1. Introduction: COVID19 and Th17

COVID19 caused by the SARS-2 coronavirus (SARS CoV2) has emerged as the third major lower respiratory tract coronavirus infection in the 21st century, after severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The hallmark of each of these infections is a viral pneumonia accompanied by host inflammation leading to pulmonary edema and a syndrome that resembles acute respiratory distress syndrome (ARDS) [1]. New information has highlighted a critical role for host Th17 inflammatory responses in the pathogenesis of COVID19 pneumonia and edema [2]. This includes the release of key cytokines including IL-17 and GM-CSF [2], and other elements of exacerbating viral immunopathogenesis through downregulating Treg cells, promoting neutrophil migration, but simultaneously inducing Th2 responses [2,3]. Importantly, IL-17 can also induce pulmonary eosinophilic responses and allergic disease, in part by promoting eosinophil production from the bone marrow and recruitment and extravasation into the lungs [4–6].

Th17 cells differentiate in part through the actions of IL-6 [7], and IL-6 has been shown to have an important role in the lung pathology associated with SARS infection [8]. There is additional evidence to suggest the SARS N protein is a potent inducer of IL-6 responses, and may mediate coronavirus lung pathology [9].

Although confirmatory studies have yet to be performed, IL-6 induced by the presence of coronaviruses in the lung appears to promote in susceptible hosts Th17 responses that may lead to severe lung pathology that includes eosinophilia. These findings potentially

provide a rational basis for evaluating anti-IL-6 monoclonal antibodies as new therapies for COVID19 [10]. In addition, IL-8 production is also generated under Th17-polarizing conditions [11].

2. Immune enhancement and coronavirus vaccines

Beyond direct virus-induced pathology, immune enhancement associated with eosinophilic infiltration and immunopathology is a potential safety concern linked to first-generation vaccines to prevent severe acute respiratory syndrome (SARS) [12]. A similar phenomenon may have derailed early efforts to develop an inactivated whole virus human vaccine against respiratory syncytial virus (RSV) [13].

The mechanisms of immune enhancement from SARS vaccinations are still not well understood. In some cases, they have been postulated as a component of antibody-dependent enhancement (ADE) seen in several other human viral infections such as dengue fever [14], while others differentiate eosinophilic immunopathology from ADE. A key element of eosinophilic immunopathology is the appearance of inflammatory infiltrates comprised of mononuclear cells, especially eosinophils, in histopathologic sections of the lungs or livers of vaccinated experimental animals, following live virus challenge. The prominence of lung eosinophils has led some investigators to conclude that immune enhancement occurs through Th2-type immunity [15]. Indeed, a document titled “Consensus considerations on the assessment of the risk of disease enhancement with COVID-19 vaccines: Outcome of a Coalition for Epidemic Preparedness from the CEPI alliance (<https://taskforce.>

[org/brighton-collaboration-cepi-covid-19-web-conference/](https://brighton-collaboration-cepi-covid-19-web-conference/); <https://brightoncollaboration.us/brighton-collaboration-cepi-covid-19-web-conference/>), has questioned the use of alum and other adjuvants that might promote Th2 responses.

However, some of the published literature argues against the primary role of Th2 cells in directly promoting immune enhancement [16]. For example, alum actually diminishes immune enhancement in laboratory animals vaccinated against the SARS coronavirus using either inactivated virus or virus-like particle vaccines [17,18]. We have made a similar observation with a recombinant protein receptor binding domain vaccine [19].

Moreover, immune enhancement occurs primarily following the use of virus-vectored vaccines, especially using vaccinia constructs expressing coronavirus antigens [20–24]. In at least one study, mice exhibiting immune enhancement following SARS virus challenge were noted to upregulate their Th1 cytokines and downregulate their anti-inflammatory cytokines such as IL-10, despite exhibiting eosinophilic infiltrates [24], although another study concluded lack of adequate Th1 induction was responsible [25].

Aside from mixed Th1 and Th2 responses, could Th17 responses also explain coronavirus-vaccine immune enhancement (Fig. 1)? While vaccinia and other vectored vaccines induce substantial immune enhancement in both the lungs and liver of experimental animals [20–24], which in some cases have been linked to viral expression of the N protein [15], none of these studies specifically examined Th17 responses. However, it is notable that immune enhancement is linked to both IL-6 and IL-8 production [22,24], each a prominent cytokine associated with Th17, as well as many other types of immune responses.

As highlighted above, the presence of eosinophilic immunopathology can be linked to Th17 responses [4–6]. While commonly thought of as the product of Th2 responses, numerous studies confirm that tissue eosinophilia can also fall under the control of Th17 responses. IL-17 and Th17 induction promote eosinophilic activation and infiltration [15], and eosinophil extravasation from the bone marrow into the lungs [4]. Moreover, eosinophilia has been shown to be sustained by Th17 cells [26,27].

3. Heart disease

Despite these concerns, notwithstanding the fact that COVID-19 involves severe pulmonary dysfunction, there remains the unknown contribution of cytokine storm, enhanced Th17 responses, or pulmonary eosinophilia to end-stage mortality [28]. Indeed, evidence increasingly suggests that severe morbidity and mortality as seen during COVID-19 may have far more to do with heart dysfunction than pulmonary failure [29,30]. Severe heart failure could in

fact be the main cause of respiratory and other organ system failure in severe, life-threatening disease. In this respect, heart failure from myocarditis and cardiomyopathy has also been linked to IL-17 producing T cells and IL-17-promoting cytokines [31].

4. Concluding comments

More research is needed into the underlying mechanisms of eosinophilic immunopathology associated with coronavirus vaccines and the relevance of this observation to clinical outcomes. However, the potential role of Th17 responses has a number of implications in terms of the production and clinical development of COVID-19 vaccines. These include adjuvant selection and vaccine dose and route. Implicating Th17 also can also inform on the selection of the safest vaccine strategy among the virus-vectored and nucleic acid-based platforms, as well as recombinant protein subunit vaccines. Such decisions will be validated in the coming months as several vaccines for COVID-19 enter the clinical pipeline and undergo extensive evaluation for both efficacy and safety. In addition to the possibility of Th17 and eosinophil-dependent immunopathology, future COVID-19 vaccine studies might focus on the cardioprotective effects of vaccination.

Declaration of Competing Interest

MEB and PJH have developed subunit vaccines against SARS and MERS coronavirus infections. They are involved in the process of developing a vaccine against SARS-CoV-2. DBC is a scientific advisor and holds intellectual property in Atropos Therapeutics, LLC.

References

- [1] Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. *J Am Med Assoc* 2020 Mar 11. <https://doi.org/10.1001/jama.2020.3633> [Epub ahead of print].
- [2] Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect* 2020. <https://10.1016/j.jmii.2020.03.005> [Epub ahead of print].
- [3] Hoe E, Anderson J, Nathanielsz J, Toh ZQ, Marimla R, Balloch A, et al. The contrasting roles of Th17 immunity in human health and disease. *Microbiol Immunol* 2017;61:49–56.
- [4] Murdock BJ, Falkowski NR, Shreiner AB, Sadighi Akha AA, McDonald RA, White ES, et al. Interleukin-17 drives pulmonary eosinophilia following repeated exposure to *Aspergillus fumigatus* conidia. *Infect Immun* 2012;80:1424–36.
- [5] Cheung PF, Wong CK, Lam CW. Molecular mechanisms of cytokine and chemokine release from eosinophils activated by IL-17A, IL-17F, and IL-23: implication for Th17 lymphocytes-mediated allergic inflammation. *J Immunol* 2008;180:5625–35.
- [6] Al-Ramli W, Prefontaine D, Chouiali F, Martin JG, Olivenstein R, Lemiere C, et al. T(H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. *J Allergy Clin Immunol* 2009;123:1185–7.
- [7] Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol* 2010;40:1830–5.
- [8] Zhang Y, Li J, Zhan Y, Wu L, Yu X, Zhang W, et al. Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infect Immun* 2004;72:4410–5.
- [9] Zhang X, Wu K, Wang D, Yue X, Song D, Zhu Y, et al. Nucleocapsid protein of SARS-CoV activates interleukin-6 expression through cellular transcription factor NF- κ B. *Virology* 2007;365:324–35.
- [10] Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv* 2020;4:1307–10.
- [11] Gasch M, Goroll T, Bauer M, Hinz D, Schutze N, Polte T, et al. Generation of IL-8 and IL-9 producing CD4(+) T cells is affected by Th17 polarizing conditions and AHR ligands. *Mediat Inflamm* 2014;182549. 2014.
- [12] Jiang S, Bottazzi ME, Du L, Lustigman S, Tseng CT, Curti E, et al. Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome. *Expert Rev Vaccines* 2012;11:1405–13.
- [13] Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. *Am J Epidemiol* 1969;89:405–21.

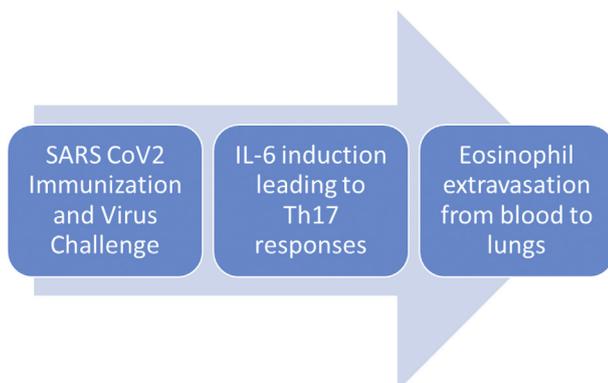


Fig. 1. Mechanisms of eosinophilic immunopathology linked to viral-vectored coronavirus vaccines.

- [14] Smatti MK, Al Thani AA, Yassine HM. Viral-induced enhanced disease illness. *Front Microbiol* 2018;9:2991.
- [15] Bolles M, Deming D, Long K, Agnihothram S, Whitmore A, Ferris M, et al. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. *J Virol* 2011;85:12201–15.
- [16] Hotez PJ, Bottazzi ME. Developing a low-cost and accessible COVID-19 vaccine for global health. [preprints.org; 2020. 2020030464](https://preprints.org/2020/2020030464).
- [17] Tseng CT, Sbrana E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. *PLoS One* 2012;7:e35421.
- [18] Iwata-Yoshikawa N, Uda A, Suzuki T, Tsunetsugu-Yokota Y, Sato Y, Morikawa S, et al. Effects of Toll-like receptor stimulation on eosinophilic infiltration in lungs of BALB/c mice immunized with UV-inactivated severe acute respiratory syndrome-related coronavirus vaccine. *J Virol* 2014;88:8597–614.
- [19] Chen WH, Tao XR, Peng BH, Pollett J, Strych U, Bottazzi ME, et al. Yeast-expressed SARS-CoV recombinant receptor-binding domain (RBD219-N1) formulated with alum induces protective immunity without significant eosinophilic immune enhancement. 2020. Unpublished manuscript.
- [20] Weingartl H, Czub M, Czub S, Neufeld J, Marszal P, Gren J, et al. Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. *J Virol* 2004;78:12672–6.
- [21] Czub M, Weingartl H, Czub S, He R, Cao J. Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets. *Vaccine* 2005;23:2273–9.
- [22] Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* 2019;4:e123158.
- [23] Deming D, Sheahan T, Heise M, Yount B, Davis N, Sims A, et al. Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. *PLoS Med* 2006;3:e525.
- [24] Yasui F, Kai C, Kitabatake M, Inoue S, Yoneda M, Yokochi S, et al. Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV. *J Immunol* 2008;181:6337–48.
- [25] Honda-Okubo Y, Barnard D, Ong CH, Peng BH, Tseng CT, Petrovsky N. Severe acute respiratory syndrome-associated coronavirus vaccines formulated with delta inulin adjuvants provide enhanced protection while ameliorating lung eosinophilic immunopathology. *J Virol* 2015;89:2995–3007.
- [26] Dias PM, Banerjee G. The role of Th17/IL-17 on eosinophilic inflammation. *J Autoimmun* 2013;40:9–20.
- [27] Keely S, Foster PS. Stop press: eosinophils drafted to join the Th17 team. *Immunity* 2015;43:7–9.
- [28] Ma WT, Yao XT, Peng Q, Chen DK. The protective and pathogenic roles of IL-17 in viral infections: friend or foe? *Open Biol* 2019;9:190109.
- [29] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020. <https://doi.org/10.1001/jamacardio.2020.1017> [Epub ahead of print].
- [30] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in wuhan, China. *JAMA Cardiol* 2020. <https://doi.org/10.1001/jamacardio.2020.0950> [Epub ahead of print].
- [31] Myers JM, Cooper LT, Kem DC, Stavrakis S, Kosanke SD, Shevach EM, et al. Cardiac myosin-Th17 responses promote heart failure in human myocarditis. *JCI Insight* 2016;1:e85851.

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