COVID-19

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Circulating spike protein may contribute to myocarditis after COVID-19 vaccination

The rapid development and emergency approval of mRNA-based vaccines have proven instrumental in reducing disease severity and mortality from SARS-CoV-2 infection. The vaccines consist of liposomally protected mRNA transcripts that encode the SARS-Cov-2 spike protein — the protein that mediates entry of the virus into host cells via the receptor ACE2 (angiotensin-converting enzyme 2). In rare cases (about 2 per 100,000), people develop myocarditis after vaccination; the frequency is relatively higher in young male patients. Previous studies have hypothesized that this may be due to an excessive immune response in genetically predisposed participants; the effect of hormones — specifically testosterone — in altering T cell immune response; or potential molecular mimicry between spike protein and endogenous antigens that elicits cardiac-targeted autoantibodies. However, the immunopathological causes of myocarditis after COVID-19 vaccination remain unclear.

In a recent study, Yonker et al. presented the results of extensive immune profiling of 16 patients hospitalized for myocarditis after mRNA vaccination against COVID-19, compared with that of 45 healthy, asymptomatic, age-matched control participants, at 3 weeks after the second vaccination dose. The participants included in the study were mostly male (80% of the myocarditis cohort; 40% of the control cohort) and mostly between 12 and 21 years of age, and most of the patients developed myocarditis within a week after the second vaccine dose. The authors found no difference in the antibody responses (antibody serotypes and function) of the two cohorts or significant differences in T cell responses. However, the participants with post-vaccine myocarditis presented a cytokine profile indicative of innate immune cell activation, an increase in neutrophils, and a decrease in platelets compared with the profile of the asymptomatic cohort. To identify the potential stimuli for this innate inflammation, the authors used ultra-sensitive single-molecule array antigen assays to detect the levels of spike protein and cleaved spike protein (S1) in free form or bound to antibodies. They found that antibody-bound S1 protein could be detected in about 30% of the two cohorts of vaccinated adolescents but in none of the analyzed adults from a separate cohort ($n = 13$; >18 years of age) after the second vaccine dose; this suggested an age difference in the processing and clearance of the spike protein translated from the mRNA vaccine, which will need to be confirmed with further investigation of a larger number of participants.

The most compelling difference in adolescents who developed post-vaccine myocarditis compared with the asymptomatic cohort was the presence of a surprisingly high level of full-length unbound spike protein that remained detectable for up to 3 weeks after vaccination and somehow eluded antibody recognition despite the lack of significant differences between the two groups in antibody production and neutralization capacity. It remains unclear if spike protein has a direct role in the pathogenesis of myocarditis; furthermore, it was detected in the majority of but not all patients with myocarditis. As myocarditis has also been observed in response to other vaccines, such as vaccines against influenza and smallpox, and non-mRNA vaccines against COVID-19, the circulating spike protein could be a biomarker of immune dysregulation leading to myocarditis, rather than a causal agent of this. On the other hand, in vitro evidence suggests that spike protein could impair pericyte and endothelial cell function via ACE2 and thus contribute to myocarditis.

In summary, this study shows potential age-related differences in the processing of vaccine-derived spike protein that may explain the relatively higher frequency of myocarditis in adolescents and young adults, and a potential role for unbound circulating spike protein in the myocarditis, which suggests that for patients in whom spike antigenemia is detected, administration of antibodies to spike protein could potentially prevent or reverse the pathology. However, given the relatively small number of participants analyzed in this study, these conclusions need to be confirmed in large cohorts.

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