RESEARCH HIGHLIGHT

Innovative adjuvant augments potency of a SARS-CoV-2 subunit vaccine

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New adjuvants that potently improve vaccine efficacy with extremely low toxicity are urgently needed. In a recent study in *Cell Research*, Liu et al. show that a new STING agonist CF501 facilitates a SARS-CoV-2 subunit vaccine to elicit robust neutralizing antibody response against several subtypes of sarbecovirus and protects experimental animals from SARS-CoV-2 infection.

The frequent emergence and rapid transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have led to severe burdens on public health systems and social panic.[1] High titers of neutralizing antibodies (nAbs) after vaccination play a critical role in limiting viral transmission and alleviating disease severity. Decreased vaccine protection against highly transmitted VOCs, notably the initial beta variant, and now the Omicron variant, has been reported in 3-dose vaccinated hosts, even a few months after vaccination.[2,3] Adjuvants are the essential elements of vaccines to enhance the strength and the properties of immune responses of the protein antigens with weak immunogenicity. While Alum, the most commonly used adjuvant, is pre-made and safe, its potency is limited, especially for cytotoxic T cells. Most adjuvants that can dramatically enhance the immunogenicity of protein antigens are usually too toxic for preventive vaccines.[4] Recently, the cyclic guanosine monophosphate (GMP) adenosine monophosphate (AMP) synthase stimulator of interferon genes (cGAS-STING) pathway was discovered. STING signaling bridges innate and adaptive immunities, and agonists of the cGAS-STING pathway are employed as vaccine adjuvants.[5,6] Although many STING agonists, such as cGAMP, CDN, and diABZI, have been shown to function as immunostimulants in preclinical studies, none of them are approved for human vaccine adjuvants because toxicity cannot be ignored for use as preventive vaccines.

In a recent study, Liu et al.[7] compared STING agonists with several well-known adjuvants, such as Alum and cGAMP. They found that the STING agonist CF501-adjuvanted RBD-Fc vaccine (CF501/RBD-Fc) elicited significantly stronger nAb and T cell responses than Alum- and cGAMP-adjuvanted RBD-Fc vaccine in mice. Intriguingly, CF501 helps elicit immunity to SARS-COV-2 RBD that cross-react with other RBDs from different sarbecovirus subtypes, but Alum and cGAMP cannot. As such, this adjuvant can play a critical role in eliciting a broader spectrum of anti-RBD against SARS-CoV-2 variants or sarbecovirus. The mechanism underlying CF501-elicited vaccine efficacy and broad antibody spectrum remains undetermined. For example, it is unclear whether CF501 helps induce antibodies that recognize different epitopes from other adjuvants. It is important to explore whether CF501 preferentially targets dendritic cells or macrophages that are essential for vaccine-induced immune responses. Currently, high-throughput single-cell RNA sequencing has been extensively applied to trace monoclonal antibody affinity shifting and maturation.[8] It would be interesting to explore whether CF501/RBD-induced antibodies have higher avidity with broader antibody spectrum or advanced maturation of specific BCR clones with higher affinity. It will also be constructive to determine whether CF501/RBD-Fc anti-sera can efficiently neutralize the Omicron variant.

The authors tested the responsiveness of CF501 in different animal models after screening with the human monocyte cell line THP-1. It seems that mice, rabbits, and rhesus macaques all respond to CF501. Each strain of the animal model has the same genetic background. In contrast, humans have distinct genetic backgrounds and HLA polymorphisms and may respond differently to the same STING agonist. Some potent anti-tumor STING agonists in mice, such as DMXAA, failed to activate human STING.[9] On the other hand, abnormal STING activation can lead to inflammation and autoimmune diseases.[10] Thus, STING is a dangerous signaling pathway that requires serious caution. It remains to be determined whether CF501 maintains lower toxicity among the diverse human populations compared to other potent adjuvants. The non-nucleotide small-molecule STING agonists are relatively stable. However, dissemination from the inoculation site may lead to systemic toxicity and other adverse effects. Indeed, a high level of CF501 in serum from the vaccinated mice could be observed, although its half-life is short. This evidence highlights the need for using targeted delivery systems to improve CF501's stability in vivo and target dendritic cells in draining lymph nodes. Because STING is localized in the cytosol, nanoparticle-carried STING-adjuvanted vaccine may increase intracellular delivery besides improving safety.[11] Such studies may optimize the adjuvanticity of STING agonists and the immunogenicity of pan-sarbecovirus subunit vaccines.

In summary, CF501 is a newly discovered STING agonist with distinct features for the SARS-CoV-2 RBD-Fc subunit vaccine. CF501 potentiates the development of effective vaccines, such as a novel pan-sarbecovirus vaccine. Further investigations of CF501 are essential to provide critical information for its clinical application to ascertain optimum potency, balanced immunogenicity, and accurate evaluation of side effects in diverse human populations.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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