

# Multisystem inflammatory syndrome in children (MIS-C): The role of viral superantigens in COVID-19 disease

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## Introduction

Superantigens are viral or bacterial virus proteins that can specifically activate a large ratio of T cells. In contrast to classic peptide antigen recognition, superantigens do not require processing in small peptides, but act as fully or partially processed proteins. They can bind to class II molecules of the main histocompatibility complex and stimulate T cells that express certain beta chains of the T cell recipient V. The other polymorphic parts of the T cell receiver, which are important for classical antigen recognition, are not important for this interaction. When this strategy is used, much of the host's immune system can be activated shortly after infection. The activated cells exhibit a variety of antigenic accuracy. The ability to stimulate polyclonal B (IgG) and T cell responses opens up the possibility of a role of superantigens in the induction of autoimmune diseases. Superantigens have been a great tool in the hands of immunologists to uncover some of the basic mechanisms of tolerance and immunity. Superantigens could play a major role in COVID-19 viral disease in children and is described as a new entity as MIS-C [1-7].

## Superantigens and COVID-19

An analysis showed that the T678NSPRRAR685 segment forms a supposedly superantigenic core that is consistently targeted against various bacterial or viral SAGs with or without the involvement of the adjacent amino acids. The combined broader sequence and structure analysis in this study, however, showed an even more convincing feature: this supposedly superantigenic SAG core, which was combined with the multi-base segment PRRAR from SARS CoV-2 S forms a highly stable salt bridge, similar to the salt bridge observed with SEB (but not with SARS1 S). The SEB superantigen peptide Y150NKKKKATVQELD161 has been reported to bind to CD28 [8], a T cell receptor that provides co-stimulatory signals necessary for T cell activation and survival. CD28 and TCRV domains share the same (immunoglobulin) fold, and the binding mechanism is likely to be adopted with minor rearrangements to allow SEB to bind to CD28.

SARS-CoV-2 peak retains other superantigenic or toxic fragments observed in the SARS1 peak including an ICAM-1 like motif involved in stabilization interactions with TCRV $\alpha$ . The existence of the potential superantigenic, toxic or intercellular adhesion molecule (ICAM)-like consequence fragments in SARS1 has been thoroughly investigated by Li, including after the 2003 pandemic. This has led to the identification of the nine sequelae including three nerve toxin type D or precursors of botulinum and two motifs that are highly similar to interstitial attachment molecule 1 (ICAM-1). Comparative analysis with the SARS-CoV-2 peak sequence revealed that seven of these sequence motifs are obtained between SARS-CoV and SARS-CoV-2. Note that ICAM-1 involvement is critical to mediate protected and inflammatory responses. Specifically, N280-E281-N282 and T286, which is closely associated with the ICAM-like fragment, interact with TCRV $\alpha$  CDRs; mainly T286 makes close contact with S94 (CDR3), E281 forms a hydrogen band with T51 (CDR2), and N280 and N282 interact closely with R69. A rare change, D839Y/E, recently observed in a SARS2 exposure of Europe, helps to stabilize the interaction with TCR. Interestingly, the SARS-CoV-2 peak binding area

hosts three residues that have recently been reported to have changed in new exposures from Europe and the USA: D614G, A831V and D839Y/N/E). The former two can potentially interact with MHCII; while the latter (D839, euro - pean claim) is located near TCRV $\beta$  and interacts strongly with N30. Its replacement by glutamate in mutant D839E increases the strength between - molecular (and thus viral T-cell) union. Even stronger interactions between the tip and TCRV $\beta$  are whether - served after replacing D839 with a tyrosine.

## Discussion

An understanding of the immunopathology that causes severe manifestations of COVID-19 in both adults and children is essential for effective treatment and management of the disease. MIS-C shows a remarkable similarity to pediatric TSS [9-13]. Using silico modelling and analysis, we found that SARS-CoV-2 encodes a superantigen motif near its S1/S2 cleavage site. This region is very similar in structure to the SEB SAg motif, which interacts with both TCR and CD28 and mediates TSS. SEB enables the activation and proliferation of T cells on a large scale [14], resulting in massive production of pro-inflammatory cytokines including IFN $\gamma$ , TNF $\alpha$  and IL-2 from T cells and IL-1 and TNF $\alpha$  from APCs [14]. This cytokine storm leads to damage to the tissue of several organs, similar to what is now observed in MIS-C. We therefore suggest that MIS-C observed in COVID-19 patients can be mediated by the superantigenic activity of the SARS-CoV-2 S protein.

So far, MIS-C is mainly observed in Europe and on the east coast of North America and is not described in Asia despite significant outbreaks of COVID-19 [9-13] (CDC and ECDC). We show that a mutation at D839 found in a European SARS CoV-2 strain increases the binding affinity of the SAg motif to the TCR. This could (at least partially) explain the geographical shift of MIS-C to areas where the European strain is endemic, and the identification of other strain-specific mutations may help to predict where a future outbreak of MIS-C may occur.

Former studies suggest the exciting possibility that immunomodulatory treatment options for TSS may also be effective for MIS-C, including IVIG and steroids. Indeed, initial published and unpublished reports suggest that MIS-C patients with or without steroids respond well to IVIG [9-11]. IVIG recognizes SEB epitopes and can therefore function partially by neutralizing a superantigen. Given structural similarities between SEB and the S-protein SAg motif, there is a possibility of cross-reactivity of these immunoglobins, which at least partially explains the response of MIS-C cases to IVIG. Other FDA-approved anti-inflammatory drugs that have been tested in SEB-TSS models may also be effective, including CTLA4-Ig, which can inhibit CD28 co-stimulation, and the existing mTOR inhibitor rapamycin in use for COVID-19. In addition, humanized anti-SEB monoclonal antibodies have been described that may also be of potential therapeutic benefit in MIS-C patients. In particular, it was shown in the mouse model of TSS that a mild SEB superantigen challenge can be prevented by short peptide mimetics of its superantigen motif. It would be interesting to investigate whether short peptide mimetics of the SARS-CoV-2 spike superantigen region could be used to prevent/attenuate the induction of inflammatory cytokine genes and toxic shock in MIS-C patients.

Unfortunately, severe respiratory manifestations of COVID-19

in children and the development of MIS-C are rare. This can have the following causes: trained immunity or cross-viral immunity to other strains of coronavirus. T and B cells play an important role in the antiviral response. CD4<sup>+</sup> and CD8<sup>+</sup> T cells from convalescent COVID-19 patients can recognize a number of SARS2 epitopes, and the S protein is a major target. Interestingly, T cells from unexposed individuals can also respond to S-protein epitopes from SARS-CoV-2, which supports the hypothesis of cross-viral immunity from other strains of coronavirus. However, why only a fraction of the infected children develop MIS-C is unclear. It is possible that a weak initial antibody response to the virus cannot neutralize the SAg, resulting in immune enhancement that leads to re-exposure, or that certain types of HLA bind the binding SAg more freely, and indeed has been shown that HLA plays a role in COVID susceptibility [16]. Of the nine cases originally reported in Great Britain, six were of Afro-Caribbean origin, which also indicates a potential genetic component of the susceptibility.

It is interesting to note that about a third or less of MIS-C patients tested positive for SARS-CoV-2, but the majority (but not all) have serological signs of infection or a history of exposure to COVID-19 [9-11]. This could indicate that the SARS-CoV-2 SAg causes a delayed hyperinflammatory response in certain children. SAg was involved in autoimmunity by triggering self-reactive T cells [17]. Antibody-mediated enhancement upon renewed exposure to the virus can also contribute to uncontrolled infection and inflammation [18]. It is also possible that the virus is still present in the gastrointestinal tract despite a negative nasopharyngeal PCR test [19]. MIS-C patients have unusually severe GI symptoms, abdominal pain, vomiting and diarrhea, in addition to severe myocardial dysfunction and cardiac shock, and such severe GI symptoms are often associated with SAg [20].

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