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Spotlight

The Mystery of MIS-C Post-SARS-CoV-2 Infection

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Following emergence of the coronavirus disease 2019 (COVID-19) pandemic, a surge in the life-threatening illness now termed 'multisystem inflammatory syndrome in children' (MIS-C) has raised questions about the unique effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children and adolescents. Two important new studies by Consiglio *et al*. and Gruber *et al*. have begun to shine light on the immune drivers of this enigmatic disease.

Early in the COVID-19 pandemic, epidemiological data offered reassuring evidence that children are largely spared of severe sequelae of SARS-CoV-2. Although that remains true, the severe MIS-C syndrome occurs in an estimated two per 100 000 children, based on New York State numbers [1], and primarily affects school-aged children approximately 4–6 weeks after the peak of total COVID-19 cases in a given region. Since April 2020, over 1000 cases of MIS-C have been confirmed by the Centers for Disease Control in the USA alone, and the clinical features of disease are now well established. MIS-C is characterized by fever and multiorgan dysfunction (including gastrointestinal, cardiovascular, cutaneous, neurologic, respiratory, nephrological, hepatologic) with the need for hospitalization in an intensive care unit in up to 80% of patients and a mortality rate of 2% [2,3]. Most children respond well to anti-inflammatory drugs (steroids, intravenous immunoglobulin, and various biologics) and supportive therapy, though a systematic evaluation of best treatments is currently lacking. To date, the pathophysiology of MIS-C remains enigmatic.

Due to a common presentation with rash, myocardial involvement, and coronary aneurisms, MIS-C has been compared extensively with Kawasaki disease (KD) [3]. Nevertheless, MIS-C is distinct from KD in several important epidemiological and clinical regards. Compared with KD patients, MIS-C patients are generally older (median of 8–11 years for MIS-C and 3 years for KD), predominantly Hispanic/Latino or Black (whereas KD is more prevalent in patients of Asian descent), and feature more pronounced abdominal symptoms, leukopenia, and elevated B-type natriuretic peptide, troponin, C-reactive protein, and ferritin [3–6]. Similarly to classical KD, MIS-C is thought to be a postinfectious inflammatory episode that is not known to recur, and no cases of MIS-C have been reported in multiple children from the same family. The unpredictable development of MIS-C in otherwise healthy children remains poorly understood, and further research is urgently needed.

What do we know about MIS-C immunopathology? Large clinical studies have consistently pointed to upregulation of systemic inflammatory cytokines in MIS-C as in other cytokine storm syndromes. Serum profiling of MIS-C patients has revealed elevated interleukin-1β (IL-1β), IL-6, IL-8, IL-10, IL-17, and interferon-gamma (IFN-γ) [7]. Consiglio *et al*. directly compared cytokines in KD and MIS-C patients and found that KD patients have higher soluble IL-6, IL-17A, CXCL10, and markers specifically associated with arteritis and coronary artery disease, compared with MIS-C patients, possibly indicating more diffuse endothelial involvement in the latter [6]. Gruber *et al*. further characterized the increased cytokines and chemokines in MIS-C as being associated with activation and recruitment of innate and adaptive immune cells via CCL19, CXCL10, CDCP1, CCL3, CCL4, EN-RAGE, and colony-stimulating factor (CSF)-1 [8]. Also elevated are markers of negative feedback on immune cells [soluble programmed death-ligand 1 (PD-L1), leukemia inhibitory factor receptor (LIF-R), IL-18R1, and hepatocyte growth factor (HGF)] and cytokines associated with mucosal immunity (IL-17A, CCL28, and CCL20) [8]. Of note, many of these cytokine profiles are not exclusive to MIS-C and are also observed in subjects with COVID-19. Furthermore, both severe COVID-19 and MIS-C patients develop neutralizing anti-SARS-CoV-2 antibody responses [6,8,9]. COVID-19 patients have higher IL-7 and IL-8, while MIS-C patients have increased IL-10, tumor necrosis factor-alpha (TNFα), soluble complement C5b9, as well as misshapen/fragmented red blood cells (burr cells and schistocytes) on peripheral blood smear, suggestive of potential vascular involvement [6,9]. In summary, MIS-C is unique compared with KD and COVID-19.

Flow cytometric immunophenotyping of MIS-C has revealed that lymphopenia affects T and B cells, with decreased frequencies of CD4, CD8, γδ T cells, and B cells [7]. Moreover, human leukocyte antigen-DR (HLA-DR) on γδ and $CD4^+CCR7^+$ T cells, and CD64 (FcγRI) on neutrophils and monocytes, were elevated [7], indicating an activated phenotype. By contrast, decreased expression of HLA-DR and CD86 was observed on monocytes and dendritic cells [7], consistent with reduced antigen-presenting capacity of innate cells that we speculate may be part of a postinflammatory feedback response. Consiglio *et al*. shed further light on possible skewing of effector T cell subsets using flow cytometry to define higher effector memory CD4 T cells and lower peripheral T follicular helper (Tfh) cells in MIS-C compared with healthy pediatric controls [6]. Using mass cytometry, Gruber *et al.* report decreased $CD16^+$ monocytes, plasmacytoid dendritic cells, $CD56^{lo}$ natural killer (NK) cells, and γδ

T lymphocytes, with an overall undisturbed distribution of naïve and effector B and T cell populations in MIS-C compared with healthy pediatric controls [8]. Neutrophils and nonclassical monocytes from MIS-C patients showed elevated CD64 (FcγRI), as reported previously [7], and higher CD54 (ICAM1), both consistent with myeloid cell activation.

Autoantibodies have been implicated in KD [10], and several research groups have looked for autoreactive antibodies in MIS-C patient serum or plasma. Using panels of human antigens (protein arrays) to screen for autoantibodies, Consiglio *et al*. and Gruber *et al*. both highlight the presence of autoantibodies in acute MIS-C patients [6,8]. Although the overall antibody binding to human peptide antigens in MIS-C is similar to that in healthy pediatric controls, KD, and pediatric COVID-19 [6], there are distinct antibody targets that distinguish MIS-C patients in each cohort. Consiglio *et al*. report increased anti-endoglin (expressed on endothelial cells), anti-MAP2K2 (mitogen-activated protein kinase 2), anti-casein kinase family proteins (activated in SARS-CoV-2-infected cells), and antibodies reacting against protein antigens that map to heart development and lymphocyte activation pathways [6]. Meanwhile, Gruber *et al*. highlight anti-Jo and anti-La antibodies, known to occur in autoimmune diseases, as well as antibody reactivity against proteins involved in immune regulation, endothelial cell function, and gastrointestinal biology [6.8]. Although triggering of autoimmune responses by SARS-CoV-2 infection is an attractive hypothesis to explain tissue damage and inflammation in MIS-C, the role of autoantibodies in pathogenesis is yet to be determined. The next step for defining autoantibody effects is to determine if there are common autoantigens (whether protein, lipid, sugar, or other) across MIS-C cohorts that are targeted by antibodies with confirmed functional relevance using intact cells and *in situ* histological evaluation of relevant tissue samples.

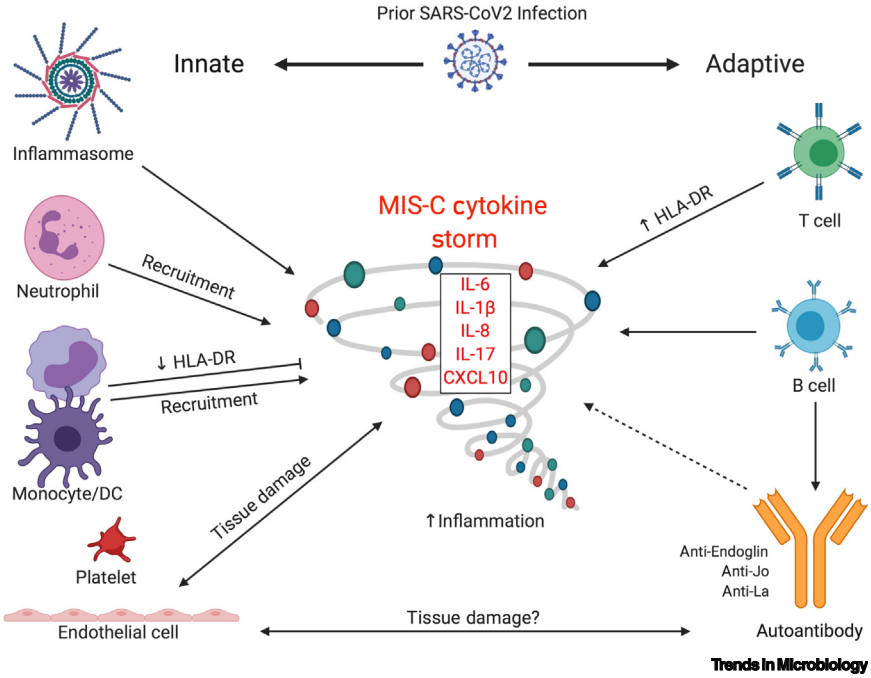

Figure 1. MIS-C Occurs 4–6 Weeks after SARS-CoV-2 Infection in Children and Adolescents and Is Characterized by a Cytokine Storm Involving Innate and Adaptive Immune Cells. The self-limiting acute inflammatory episode in MIS-C is characterized by tissue damage affecting several organ systems and the coronary arteries and is associated with potential extravasation of innate immune cells, activation of T cells, and autoantibodies. The figure was generated with Biorender.com. Abbreviations: DC, dendritic cell; HLA-DR, human leukocyte antigen-DR; IL, interleukin, MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The evolving new literature is rapidly elucidating serum and cellular phenotypes correlated with systemic inflammation in MIS-C (summarized in Figure 1). Nonetheless, much remains unknown about susceptibility factors, triggers, and mechanisms of disease in this serious, delayed complication of SARS-CoV-2 infection in children and adolescents. Whether there is a single pathophysiological mechanism or multiple MIS-C subtypes with differing drivers and outcomes remains to be determined. Further investigation is imperative to understand the pathogenesis of this disease and, in turn, to help guide its treatment and prevention as the COVID-19 pandemic continues with new waves on the horizon.

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