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## Viewpoint

# The Heart of the Problem in Multisystem Inflammatory Syndrome in Children

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**Multisystem inflammatory syndrome in children (MIS-C) is a severe, life-threatening, post-COVID-19 hyperinflammatory illness that is not yet fully understood. In this issue of *Med*, de Cevins et al. used a multi-parametric approach to define COVID-19-related disease, specifically identifying a molecular signature of the most severe form of COVID-19-related illness: MIS-C with myocarditis.<sup>1</sup>**

In the early days of the COVID-19 pandemic, when schools were shut down and families isolated themselves, children appeared to be spared from COVID-19. Then, children previously exposed to or mildly infected with SARS-CoV-2 began to be hospitalized with cardiac failure, myocarditis, and severe, life-threatening illnesses. In the US alone, over 4,400 children to date have been diagnosed with this post-COVID-19 illness, now termed Multisystem Inflammatory Syndrome in Children (MIS-C) (<https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance>). Although significant advances have been made in our understanding of the pathology associated with MIS-C,<sup>2,3,4</sup> the pathomechanism driving cardiac injury as a result of MIS-C has been poorly understood. In the article, “A monocyte dendritic cell molecular signature of SARS-CoV-2 related multi-system inflammatory syndrome in children (MIS-C) with severe myocarditis” by de Cevins et al., the authors present a rich analysis of cytokine levels, cellular profiling, and gene expression to define the inflammatory signature associated with severe myocarditis that can be seen in MIS-C, significantly advancing our understanding of the cardiac manifestations of MIS-C (Figure 1).<sup>1</sup>

In this issue of *Med*, de Cevins et al. provide a tremendous dataset charac-

terizing the inflammatory profile of 56 children with suspected SARS-CoV-2 infection or related disease plus 34 healthy controls.<sup>1</sup> This cohort included 13 children with acute infection (COVID-19 or other respiratory infections) and 43 with post-acute hyperinflammation (30 children with MIS-C with or without cardiac involvement, and 14 with Kawasaki disease [KD]). The authors analyzed plasma cytokine levels, plus both CyTOF and single-cell RNA sequencing of peripheral blood mononuclear cells to describe the immune responses, with a specific focus on distinguishing both acute infection with COVID-19 from post-acute hyperinflammatory responses seen in MIS-C and MIS-C with myocarditis from MIS-C without cardiac involvement. (Figure 1)<sup>1</sup>

The authors report considerable overlap in cytokine responses in both acute COVID-19 and MIS-C. However, MIS-C displayed higher levels of IFN- $\gamma$ , IFN- $\alpha$ 2, IL-17A, TNF- $\alpha$ , and IL-10. Additionally, both acute COVID-19 and MIS-C were characterized by a reduction in dendritic cells (DCs) and mucosal associated invariant T cells (MAITs). However, in MIS-C, immune activation was focused within the dendritic cells and monocytes, as compared to a more generalized cellular activation in acute COVID-19.

Notably, the gene expression by DCs and monocytes best characterized MIS-C and allowed a distinguishable signature in MIS-C with myocarditis. MIS-C with myocarditis showed both an increase in expression of the NF- $\kappa$ B pathway, which plays a key role in mediating inflammatory responses through induction of several pro-inflammatory genes, and a strong decrease in the expression of NF- $\kappa$ B inhibitors in all MIS-C patients. In MIS-C with severe myocarditis, the decrease in NF- $\kappa$ B inhibitors lead to sustained TNF- $\alpha$  signaling, which then contributed to the amplification of the hyperinflammatory response through regulating various inflammatory cytokines. This difference in NF- $\kappa$ B signaling inhibition may partially explain the extreme inflammation seen in MIS-C with myocarditis.

Further, MIS-C with myocarditis showed decreased type I and type II interferon responses as compared to MIS-C without cardiac involvement. This differential response was specific to monocytes and dendritic cells. This impaired response may cause suboptimal antigen presentation and reduced clearance of SARS-CoV-2 antigens, contributing to the severity of the disease through a compromised immune system. These results show the crucial role of monocytes and dendritic cells in the pathophysiology of MIS-C with myocarditis. Importantly, de Cevins et al. report 25 genes in pathways related to inflammation, oxidative stress, TNF- $\alpha$  and/or NF- $\kappa$ B signaling

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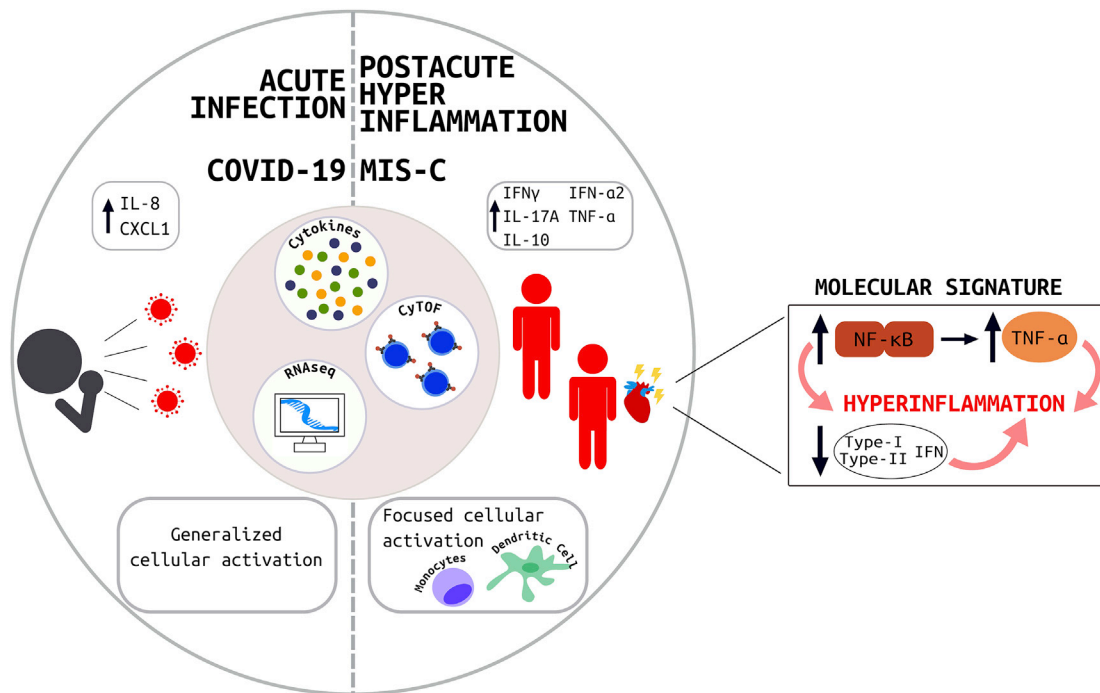
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**Figure 1. Distinct molecular signature within MIS-C with severe myocarditis**

A multi-parametric approach was utilized to study pediatric patients with acute infections and post-acute hyperinflammation related to SARS-CoV-2. Cytokines expression, cellular profiling and single cell gene expression was used. Pediatric patients with MIS-C with myocarditis showed a distinct molecular signature, including increased NF- $\kappa$ B signaling, leading to increased TNF- $\alpha$ , and low type-I and type-II interferon response. This molecular signature is distinct from acute COVID-19 and MIS-C without myocarditis.

that distinctly segregate MIS-C with myocarditis from acute infection and other post-acute hyperinflammatory responses.<sup>1</sup>

Defining the inflammatory signature associated with MIS-C myocarditis is critical, because this is the first step in understanding and identifying cardiac complications of MIS-C early, treating cardiac involvement effectively, and perhaps, allowing pathways for prevention of this severe post-COVID-19 illness. Currently, there is no predicting who will develop MIS-C. Further, of those who develop MIS-C, only two-thirds will develop cardiac involvement.<sup>5</sup> The only prerequisite for MIS-C is prior exposure to SARS-CoV-2. It is not clear what predisposes an individual to develop cardiac manifestations of MIS-C. Now, with over 4.3 million children having been diagnosed with COVID-19 in the US to date (<https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/>

[children-and-covid-19-state-level-data-report/](#)), and with the Delta variant triggering a rapid uptick in cases as schools return to session and after-school activities resume, we will undoubtedly see more cases of MIS-C in the near future. And as cases of MIS-C rise, more children will develop severe cardiac manifestations of the disease and, unfortunately, this will likely result in more MIS-C related deaths. Efforts are urgently needed to build on the dataset here to create a clinically available toolset for identifying and intervening in cardiac injury early to prevent severe disease and death in these children.

The findings reported by de Cevins et al.<sup>1</sup> raise interesting and clinically important questions. How does this molecular signature of cardiac injury change over time? It is important to note that the vast majority of the samples studied by de Cevins et al. were obtained after initi-

ation of immune-modulating therapies (such as immunoglobulin and/or steroids). Ascertaining early immune signals and gene signatures upon presentation—or better yet prior to the development of cardiac involvement—could allow the development of predictive biomarkers to guide early intervention and potential prevention of severe, cardiac complications related to MIS-C.

Additionally, we do not yet know the long-term impact of MIS-C. Although markers of cardiac injury, such as cardiac enzymes, and structural injuries including coronary arterial aneurysms appear to resolve relatively quickly in MIS-C,<sup>5</sup> it has not yet been shown whether epigenetic changes or gene expression persists, or if these individuals then are at increased risk of cardiac disease in the future. Follow up studies building on the important findings by de Cevins et al. would play a critical role in understanding the long-term

implications of COVID-19 in children and MIS-C.<sup>1</sup>

Another important question is whether post-COVID-19 vaccine myocarditis, a rare side effect of the mRNA COVID-19 vaccines, shares an underlying molecular signature with MIS-C or if the pathology is different. Most reported cases of post-vaccine myocarditis present 1–6 days after receipt of the second dose of the vaccine, have mild disease, and have shown complete recovery of cardiac function.<sup>6</sup> No coronary artery aneurysms have been reported. Although the risks of developing complications from COVID-19 across all ages significantly outweighs the risk of developing myocarditis, favoring vaccination (<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html>), it is important to build our understanding of this potential side effect. This rich dataset provided by de Cevins et al. lays the groundwork for in-depth profiling of various disease states and inflammatory responses related to COVID-19 in children.<sup>1</sup>

In summary, this rich dataset reported by de Cevins et al.<sup>1</sup> can be used to help develop clinical biomarkers to aid in the early diagnosis of MIS-C and prediction of cardiac involvement and to identify novel targets needed in developing therapeutics aimed at treating both acute and post-acute responses to SARS-CoV-2.

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### DECLARATIONS OF INTERESTS

The authors have no conflicts to declare.

1. de Cevins, C., Luka, M., Smith, N., Meynier, S., Magéus, A., Carbone, F., Garcia-Paredes, V., Barnabei, L., Batignes, M., Boullé, A., et al.; Pediatric-Biocovid Study Group (2021). A monocyte/dendritic cell molecular signature of SARS-CoV-2 related multisystem inflammatory syndrome in children (MIS-C) with severe myocarditis. *Med* 2, 1072–1092.
2. Gruber, C.N., Patel, R.S., Trachtman, R., Lepow, L., Amanat, F., Krammer, F., Wilson, K.M., Onel, K., Geanon, D., Tuballes, K., et al.

(2020). Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). *Cell* 183, 982–995.e14.

3. Porritt, R.A., Paschold, L., Rivas, M.N., Cheng, M.H., Yonker, L.M., Chandnani, H., Lopez, M., Simnica, D., Schultheiß, C., Santiskulvong, C., et al. (2021). HLA class I-associated expansion of TRBV11-2 T cells in multisystem inflammatory syndrome in children. *J. Clin. Invest.* 131, 146614. <https://doi.org/10.1172/JCI146614>.
4. Yonker, L.M., Gilboa, T., Ogata, A.F., Senussi, Y., Lazarovits, R., Boribong, B.P., Bartsch, Y.C., Loiselle, M., Rivas, M.N., Porritt, R.A., et al. (2021). Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. *J. Clin. Invest.* 131, 149633. <https://doi.org/10.1172/JCI149633>.
5. Feldstein, L.R., Tenforde, M.W., Friedman, K.G., Newhams, M., Rose, E.B., Dapul, H., Soma, V.L., Maddux, A.B., Mourani, P.M., Bowens, C., et al.; Overcoming COVID-19 Investigators (2021). Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. *JAMA* 325, 1074–1087. <https://doi.org/10.1001/jama.2021.2091>.
6. Dionne, A., Sperotto, F., Chamberlain, S., Baker, A.L., Powell, A.J., Prakash, A., Castellanos, D.A., Saleeb, S.F., de Ferranti, S.D., Newburger, J.W., and Friedman, K.G. (2021). Association of Myocarditis With BNT162b2 Messenger RNA COVID-19 Vaccine in a Case Series of Children. *JAMA Cardiol.* <https://doi.org/10.1001/jamacardio.2021.3471>.