


INFLAMMATION

Kawasaki disease and MIS-C share a host immune response

Paul Tsoukas and Rae S. M. Yeung 

Multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease are both hyperinflammatory disorders associated with infectious diseases, but are they distinct syndromes or do they exist along a continuum? A comparison of the host immune response in these illnesses provides surprising new insights.

Refers to Ghosh, P. et al. An Artificial Intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease. *Nat. Commun.* **13**, 2687 (2022).

signatures were found to be upregulated in children with Kawasaki disease in the acute phase of the disease in comparison with healthy children. Although neither signature was able to predict treatment response, both tracked with disease severity using coronary artery aneurysm size as the outcome metric. These data are consistent with the hypothesis that Kawasaki disease is triggered by various different pathogens, as the common host response to diverse pathogens is represented by the ViP and sViP signatures.

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Ghosh et al. also used the ViP and sViP gene expression signatures to compare a group of patients with Kawasaki disease with a small cohort of 10 children with MIS-C and reported that although the signatures were induced at significantly higher levels in the patients with MIS-C than in those with Kawasaki disease, they could not differentiate between those with MIS-C or Kawasaki disease, suggesting that both syndromes share a common host immune response. Similar to the findings in Kawasaki disease and COVID-19, the sViP signature was able to identify those patients with severe MIS-C, when myocardial dysfunction was used as an indicator of severity.

Ghosh et al. then employed a Kawasaki disease-specific 13-gene expression signature that had previously been used to identify those with Kawasaki disease among children presenting with fever. Interestingly, the transcripts in the Kawasaki disease-specific panel did not overlap with the ViP gene expression signatures, but this panel was likewise unable to differentiate between patients with MIS-C and those with Kawasaki disease. As expected, use of an expanded dataset with whole blood transcriptomics (RNA sequencing) and a protein panel of 10 cytokines provided a more granular dissection of MIS-C and Kawasaki disease samples and was able to differentiate and identify subgroups of patients. The expanded dataset also confirmed that the ViP signatures captured a subset of the genes that are differentially expressed between the MIS-C and Kawasaki disease subgroups,

Multisystem inflammatory syndrome in children (MIS-C) is one of several names coined to denote a SARS-CoV-2-triggered clinical presentation that shares clinical features, complications and treatment approaches with Kawasaki disease. However, whether MIS-C is a new syndrome consisting of SARS-CoV-2-mediated fever with cytokine release or is SARS-CoV-2-triggered Kawasaki disease, or some combination thereof, remains unclear. Comparisons of these conditions and international collaborative study are further complicated by the continued use of different names and case definitions across geographic regions. Using artificial intelligence approaches to explore the similarities and differences between MIS-C and Kawasaki disease, Ghosh et al.¹ compared established gene expression signatures in response to viral infections to show that these two syndromes have a shared host immune response that is suggestive of a single disease spectrum.

Kawasaki disease is a heterogeneous syndrome that is thought to be triggered by infectious agents, including coronaviruses². Children with Kawasaki disease present with marked systemic inflammation characterized by multisystem vasculitis, which self-resolves in the majority of patients within 1–2 weeks without sequelae. In some cases, Kawasaki disease is complicated by coronary artery aneurysms, shock and/or macrophage activation syndrome (MAS), which occur in 5%, 6% and 2% of patients, respectively³. MIS-C is a hyperinflammatory syndrome characterized

by multisystem inflammation triggered by an antecedent SARS-CoV-2 infection⁴. Of note, MIS-C has a more extreme phenotype than Kawasaki disease, with shock and MAS occurring in approximately 20% and 40% of affected children, respectively, but the incidence of coronary artery abnormalities is similar^{5,6}.

To define the host immune response in Kawasaki disease and MIS-C, Ghosh et al.¹ used a previously identified 166-gene signature they termed a viral pandemic (ViP) gene expression signature, which captures an invariant spectrum of the host response that is universally conserved across three respiratory viral pandemics: influenza, avian flu and now SARS-CoV-2. The ViP gene expression signature is thought to reflect a shared fundamental aspect of the host immune response to viral triggers, including broad representation of cytokine signalling and cellular processes. Interestingly, Ghosh et al. found that many transcripts in the ViP signature are in pathways related to IL-15, but that this signature is distinct from the typical interferon-responsive gene signatures. A 20-gene subset of the ViP signature, termed severe ViP (sViP) signature, was also identified using a discovery dataset from patients with influenza; the sViP signature tracked with disease severity not only in the patients with influenza in the original dataset but also in those with COVID-19.

Both the ViP and sViP gene expression signatures were tested in several cohorts of children with Kawasaki disease diagnosed prior to the COVID-19 pandemic, and both

again suggesting that MIS-C is a more extreme version of Kawasaki disease with a more exaggerated host immune response.

The overlapping immunophenotype based on viral signatures supports the hypothesis that Kawasaki disease and MIS-C are not in fact separate entities but are names describing the different ends of the spectrum of the host immune response (FIG. 1). These data highlight the tension and pitfalls between the need for rapid recognition and case surveillance, as in the early days of the COVID-19 health emergency, and the need for comprehensive phenotyping and case definitions. Case definitions derived in the early stages of the COVID-19 pandemic reflected the most severe presentations, and did not recognize

less-extreme phenotypes associated with SARS-CoV-2-triggered systemic inflammation. This omission is akin to removing Kawasaki disease-shock syndrome from the Kawasaki disease diagnosis. As a result, the differences found between MIS-C and Kawasaki disease reaffirm this self-fulfilling prophecy. The subsequent bias that affects the spectrum of disease captured has continued to skew our understanding of MIS-C. An alternative approach is to stratify post-infection hyperinflammation syndrome into subgroups on the basis of the clinical phenotype recognized at the bedside, in a manner agnostic to the infectious trigger. Such an approach would recognize the full spectrum of phenotypes and complications, including cardiogenic

shock (such as MIS-C shock and Kawasaki disease shock syndrome), MAS (cytokine storm-associated cytopenias and coagulopathies triggered by infection), Kawasaki disease (the typical, complete Kawasaki disease phenotype, triggered by SARS-CoV-2 or another infectious agent), and fever and hyperinflammation (mild or incomplete features of Kawasaki disease).

The report by Ghosh et al. provides interesting food for thought, as an appetizer with small patient numbers, in anticipation of and excitement for a main course of more comprehensive investigations involving larger, independent patient cohorts, through which we can dissect the hypothesis that Kawasaki disease and MIS-C are on the same disease spectrum.

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Competing interests

The authors declare no competing interests.

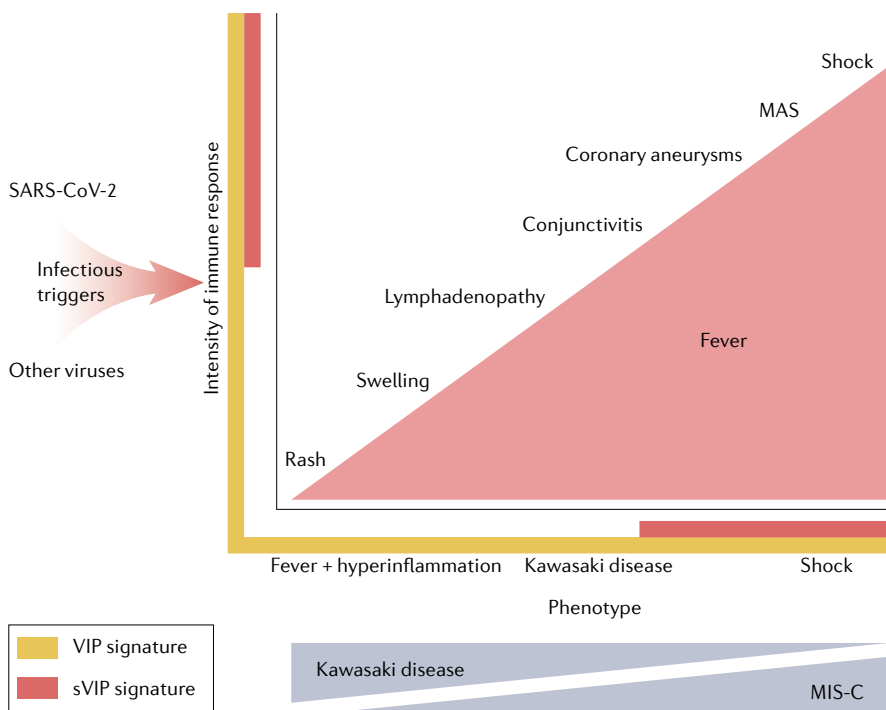


Fig. 1 | Post-infection hyperinflammation encompasses a spectrum of phenotypes. Various infectious triggers prompt an invariant gene expression signature termed the viral pandemic (ViP) signature (yellow line). The intensity of the post-infectious immune response drives the clinical phenotype, which can range from mild hyperinflammation to macrophage activation syndrome (MAS) and cardiogenic shock. Expression of a subset of the ViP signature, termed severe ViP (sVIP) signature (red line), correlates with disease severity. Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) share a similar immunobiology and phenotype with overlapping features reflecting different parts of the disease spectrum.