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“Investigating the Molecular Determinants of Multisystem Inflammatory Syndrome in Children”

By

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10:00 AM
ICPH Auditorium

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) is a severe post-infectious complication of SARS-CoV-2 characterized by systemic inflammation and multiorgan involvement. Although extensive immune dysregulation has been described during acute MIS-C, the molecular features that distinguish the syndrome from other inflammatory diseases and the host factors that predispose only a subset of infected children to develop MIS-C remain incompletely understood. This dissertation investigated these complementary aspects of MIS-C by characterizing its circulating inflammatory environment and examining the functional consequences of rare genetic variation in an innate immune signaling protein.

The first study used Olink proximity extension assays to profile 184 plasma proteins related to inflammation, immune responses, and cardiometabolic biology in 172 participants with MIS-C, mild or asymptomatic SARS-CoV-2 infection, Kawasaki disease, pneumonia, severe COVID-19, sepsis, or inflammatory gastrointestinal disease. MIS-C showed extensive differences relative to mild or asymptomatic infection but greater molecular overlap with active inflammatory diseases, with the proteins distinguishing MIS-C varying by comparator. Elastic-net modeling was used to determine whether combinations of circulating proteins could distinguish MIS-C within this inflammatory context. A five-protein signature comprising VASN, TRIM21, CXCL9, IL-12B, and PD-L1 distinguished MIS-C from the pooled inflammatory comparator group with an area under the receiver operating characteristic curve of 0.954 (95% CI, 0.916–0.992), 85.7% sensitivity, and 93.0% specificity. These findings demonstrate that MIS-C shares substantial inflammatory biology with clinically overlapping diseases while retaining a distinct combination of circulating molecular features.

The second study investigated TIRAP following the identification by collaborators in the CONNECT study of rare TIRAP variants in children with MIS-C. Functional characterization of the identified V90M, C134R, A164D, and I176M substitutions demonstrated distinct effects on NF- κ B/AP-1-responsive reporter activity despite preserved measured protein expression. V90M increased activity, C134R and A164D reduced activity, and I176M remained similar to wild-type TIRAP. Further characterization showed that V90M and A164D had stability profiles similar to wild type. A164D additionally exhibited a reduced proportion of Phos-tag-shifted species and reduced association with MYD88, linking its impaired signaling phenotype to altered post-translational regulation and adapter-complex interactions.

Together, these studies examine molecular determinants of MIS-C at two complementary levels. Plasma proteomic profiling defines features of the systemic inflammatory state after MIS-C has developed, whereas functional analysis of TIRAP demonstrates that rare host variation can alter a proximal innate immune signaling pathway. Although a direct mechanistic relationship between the TIRAP variants and the circulating protein signatures was not established, the findings support a broader framework in which MIS-C reflects both host-specific variation in immune regulation and the subsequent development of a complex systemic inflammatory state. Understanding how these levels interact may help explain the progression from a common viral infection to an uncommon post-infectious inflammatory syndrome.