**High-Dimensional Immune Profiling Identifies Cellular Correlates of SARS-CoV-2 Non-Transmission in Households**

Benjamin Dorschner[1,2,3$], Ralf Wiedemuth[1,2$], Jakob Armann[1], Nicole Töpfner[1], Catharina Schütz[1,2], Reinhard Berner[1,2], and Sebastian Thieme[1,2]

Identifying host immune features that reduce transmission of respiratory viral infections remains challenging. Using SARS-CoV-2 as a model pathogen, the COVID-19 pandemic provided an opportunity to investigate such factors within households where close proximity is given and transmission probability therefore high. We applied high-dimensional mass cytometry to characterize immune profiles of cryopreserved PBMCs from 72 individuals across 22 families with well-documented infection status confirmed by nasal PCR and/or antigen testing. PBMCs were stimulated overnight with peptide pools derived from SARS-CoV-2, endemic coronavirus NL63, or human actin (control), and analyzed using a 37-parameter CyTOF panel capturing major immune subsets and cytokine responses. To identify immune correlates of reduced transmission probability, we employed an adaptive elastic-net model integrating cell frequencies and cytokine-production profiles. The model selected four cell types and functional states—IFNγ expression of $CD4^+CD161^+$ effector memory Th2 cells, frequency of $CD8^+CD25^+$ effector memory T cells, $CD57^+$ NK cells and double negative T cells. Each predictor reflects an effector-memory or cytotoxic immune state that has been associated with rapid viral control. All predictors were specific for transmission probability, as there was no overlap with predictors of infection status. IFNγ expression of $CD4^+CD161^+$ effector memory Th2 cells exhibited the strongest correlation with SARS-CoV-2 non-transmission. This finding points towards a potential role of doubly committed Th2+1 cells in effective clearance of SARS-CoV2 infections and contributes to our understanding that $CD4^+$ T cells exist on a continuum retaining the capability to flexibly reprogram cytokine expression.

**Affiliations**

[1]Department of Pediatrics, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany;

[2]German Center for Child and Adolescent Health (DZKJ), partner site Dresden/Leipzig, Germany;

[3]Division of Respiratory and Critical Care Medicine, University of Basel Children's Hospital (UKBB), Basel, Switzerland

[$]contributed equally