

Abstract ID: 92496

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Area of Research: Immunology, microbiome research and respiratory diseases

PhD Programme: DS Sustainable Health Research (SHR)

Semester: 3

Different transcriptional responses of SARS-CoV-2 variants of concern revealed by comparative high-resolution spatial transcriptomics

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Recurrently emerging SARS-CoV-2 variants of concern (VOC) drive COVID-19 pandemic waves, as exemplified recently by the highly infective B.1.1.529 variant known as Omicron, which in general cause mild disease. Using spatial transcriptomic in Calu-3 cells infected with various VOC, we identified marked differences in the molecular host responses. We report decreased infection rates for the dominant VOC B.1.1.529 (Omicron) (27%) compared to B.1.617.2 (Delta) (63%) and the original SARS-CoV-2 strain (Wuhan-Hu-1) (43%) in Calu-3 cells. With a set of 84 immune-relevant genes, we discriminated transcriptional responses and compared immune strategies of these Omicron and Delta variants. By spatially dissecting highly virus replicating and bystander cells, we highlighted molecular signatures unique to individual VOCs. We detected a massive upregulation of NFKBIA in Wuhan-Hu-1 and B.1.617.2 infected cells, hinting at impaired interferon signalling which manifests in absent correlative gene expression in bystander cells. In contrast, NFKBIA levels in Omicron infected cultures were comparable to mock infected cells, and bystander cells accomplished correlative expression of antiviral genes, suggesting an increased cellular capability to launch a proper immune response against B.1.1.529 infection, which might prevent severe disease.