BTS/BALR/AUK-BLF Early Career Investigator Symposium

T1 THE LOCAL AND SYSTEMIC RESPONSE TO SARS-COV-2 INFECTION IN CHILDREN AND ADULTS

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Introduction and Objectives Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current coronavirus disease 2019 (COVID-19) pandemic. Whilst a substantial proportion of adults infected with SARS-CoV-2 progress to develop severe disease, children rarely manifest respiratory complications. However, the underlying mechanism behind this disparity remains largely unknown. Understanding the differences in the local and systemic response to SARS-CoV-2 infection at single cell resolution between children and adults may offer key clues about the pathogenesis of SARS-CoV-2 infection, providing guidance for future therapies and treatments.

Methods To address this we generated a healthy reference multi-omics single cell data set from children (n=30) from infancy to adulthood (n=11). Here we profiled triple matched samples: nasal and tracheal brushings and PBMCs for single cell analysis, where we tracked the developmental changes for 59 airway and 45 blood cell populations at both

transcriptomic and proteomic level. These were then contrasted with equivalent data from paediatric and adult COVID-19+ patients collected across a range of disease severities (total n=32), enabling age and disease-specific variances to be analysed at single cell level.

Results Striking differences within the paediatric and adult immune responses in COVID-19 were observed, including an overall weaker interferon-response signature, with fewer interferon-stimulated immune cell subpopulations within children infected by SARS-CoV-2 compared to adults. In peripheral blood, a greater proportion of naïve cell populations was observed with disease, with the response in adults primarily dominated by the adaptive immune system. In the airway epithelium, we found the highest viral load in goblet and ciliated cells in infected adults and most notably, described a novel inflammatory epithelial cell population, enriched within our COVID-19 patients, representing a transitional regenerative state between secretory and ciliated cells. Through the integration of matched blood and airway samples we were able to investigate the dynamics between local and systemic response to COVID-19, finding marked differences.

Conclusions Overall, this largest paediatric single cell COVID-19 study to date showed significant differences in response to SARS-CoV-2 between children and adults, reflecting the changes of the immune landscape over developmental time, which in children are dominated by naïve and innate responses.

T2 CLUSTER ANALYSIS OF TRANSCRIPTOMIC DATASETS TO IDENTIFY ENDOTYPES OF IDIOPATHIC PULMONARY FIBROSIS

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Rationale Considerable clinical heterogeneity in Idiopathic Pulmonary Fibrosis (IPF) suggests the existence of multiple disease endotypes. Identifying these endotypes could allow for

Abstract T1 Figure 1

the development of a biomarker-driven personalised medicine approach in IPF.

Objectives To improve our understanding of the pathogenesis of IPF by identifying clinically distinct groups of patients with IPF that could represent distinct disease endotypes.

Methods We systematically selected three publicly available datasets containing gene expression data measured from whole blood (220 IPF cases total). These datasets were co-normalised, pooled and clustered. We then compared clinical and demographic traits across clusters and used gene enrichment analysis to identify biological pathways and processes that were over-represented among the genes that were differentially expressed across clusters. A classifier was developed to assign additional individuals with IPF to a cluster using expression data from a minimal number of genes. We validated the classifier using three additional independent datasets (194 IPF cases total) and compared its performance at predicting survival in IPF to that of a previous transcriptomic prognostic biomarker for IPF.

Results We identified three clusters of IPF patients with distinct transcriptomic signatures. These clusters demonstrated statistically significant differences in lung function ($P=0.009$) and mortality ($P=0.009$) between groups. One cluster appeared to consist of patients with favourable lung function and survival over time (low risk cluster), whilst the other two clusters contained patients with worse lung function and reduced survival (high risk clusters). Gene enrichment analysis implicated dysregulation of mitochondrial homeostasis, apoptosis, cell cycle and innate and adaptive immunity in the pathogenesis of these groups. We developed and validated a 13-gene cluster classifier that predicted mortality in IPF (figure 1).

Abstract T2 Figure 1 Survival over time for the IPF subjects in the validation datasets, stratified by risk group according to our 13-gene classifier. The P-value on the plot is from a log-rank test testing the two curves for equality. The dashed line on the plot indicates the median survival time for the risk group if this could be calculated

Conclusions There are at least two groups of IPF patients with significant differences in survival and lung function that are discernible by blood gene expression signatures. These groups could be representative of distinct pathophysiological states, which would support the theory of multiple endotypes of IPF. Although more work must be done to confirm the existence of these endotypes, our classifier could be a useful tool in patient stratification and outcome prediction in IPF.

T3 INTEGRATED TRANSCRIPTOMIC ANALYSIS OF HUMAN TUBERCULOSIS GRANULOMAS AND A BIOMIMETIC MODEL IDENTIFIES SPHINGOSINE KINASE 1 AS A POTENTIAL THERAPEUTIC TARGET

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The global burden of tuberculosis (TB) continues at pandemic proportions, currently with a quarter of the world's population infected with *Mycobacterium tuberculosis* (Mtb), and 1.4 million people dying from TB in 2019 (WHO, 2020). Mtb has undergone prolonged co-evolution with humans, with the balance between protective and pathological host responses likely to play a key role in determining clinical severity. Sarcoidosis is another granulomatous condition primarily affecting the lung and lymph nodes. TB and sarcoidosis share histological and clinical features, which can be indistinguishable, including immune-related phenomena which suggest shared immunological processes. Despite scientific advances, the immunopathology of TB and sarcoidosis remain incompletely understood. Here, we show the combination of unbiased analysis of patient samples and a biomimetic model has established a translational pipeline to identify new therapeutic approaches.

We hypothesised that whole transcriptome analysis of human TB granulomas isolated by laser capture microdissection could identify therapeutic targets, and that comparison with sarcoidosis would identify disease-specific mechanisms.

Abstract T3 Figure 1 Mtb growth detected in 3D collagen model measured by luminescence (RLU, relative light units): untreated (black circles), DMSO (black squares), and SphK1 inhibitor PF-543 (unfilled triangles). Black arrows: drug addition on days 1 and 7. Experiments were performed on at least five occasions using PBMCs from five separate healthy donors with triplicate conditions. Data presented are from a representative donor and are consistent across donors. Analysis: two way ANOVA with Dunnett's Multiple Comparison Test, error bars: SD.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$