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北京易研科技有限公司

2021.03

10×Genomics 新冠

已发表文献集

Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment

Nature (IF: 46.49), Jul 2020, Lihong Liu et al. DOI: 10.1038/s41586-020-2571-7PubMed: 32698192
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic continues, with devasting consequences for human lives and the global economy1,2. The discovery and development of virus-neutralizing monoclonal antibodies could be one approach to treat or prevent infection by this coronavirus. Here we report the isolation of sixty-one SARS-CoV-2-neutralizing monoclonal antibodies from five patients infected with SARS-CoV-2 and admitted to hospital with severe coronavirus disease 2019 (COVID-19). Among these are nineteen antibodies that potently neutralized authentic SARS-CoV-2 in vitro, nine of which exhibited very high potency, with 50% virus-inhibitory concentrations of 0.7 to 9 ng ml-1. Epitope mapping showed that this collection of nineteen antibodies was about equally divided between those directed against the receptor-binding domain (RBD) and those directed against the N-terminal domain (NTD), indicating that both of these regions at the top of the viral spike are immunogenic. In addition, two other powerful neutralizing antibodies recognized quaternary epitopes that overlap with the domains at the top of the spike. Cryo-electron microscopy reconstructions of one antibody that targets the RBD, a second that targets the NTD, and a third that bridges two separate RBDs showed that the antibodies recognize the closed, 'all RBD-down' conformation of the spike. Several of these monoclonal antibodies are promising candidates for clinical development as potential therapeutic and/or prophylactic agents against SARS-CoV-2.

Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing

Cell (IF: 38.62), Oct 2020, Yapeng Su et al. DOI: 10.1016/j.cell.2020.10.037PubMed: 33171100
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

We present an integrated analysis of the clinical measurements, immune cells, and plasma multi-omics of 139 COVID-19 patients representing all levels of disease severity, from serial blood draws collected during the first week of infection following diagnosis. We identify a major shift between mild and moderate disease, at which point elevated inflammatory signaling is accompanied by the loss of specific classes of metabolites and metabolic processes. Within this stressed plasma environment at moderate disease, multiple unusual immune cell phenotypes emerge and amplify with increasing disease severity. We condensed over 120,000 immune features into a single axis to capture how different immune cell classes coordinate in response to SARS-CoV-2. This immune-response axis independently aligns with the major plasma composition changes, with clinical metrics of blood clotting, and with the sharp transition between mild and moderate disease. This study suggests that moderate disease may provide the most effective setting for therapeutic intervention.

Severely ill COVID-19 patients display impaired exhaustion features in SARS-CoV-2-reactive CD8+ T cells

Science (IF: 44.37), Sep 2020, Prabhu S Arunachalam et al. DOI: 10.1126/science.abc6261PubMed: 32788292
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Coronavirus disease 2019 (COVID-19) represents a global crisis, yet major knowledge gaps remain about human immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We analyzed immune responses in 76 COVID-19 patients and 69 healthy individuals from Hong Kong and Atlanta, Georgia, United States. In the peripheral blood mononuclear cells (PBMCs) of COVID-19 patients, we observed reduced expression of human leukocyte antigen class DR (HLA-DR) and proinflammatory cytokines by myeloid cells as well as impaired mammalian target of rapamycin (mTOR) signaling and interferon-α (IFN-α) production by plasmacytoid dendritic cells. By contrast, we detected enhanced plasma levels of inflammatory mediators-including EN-RAGE, TNFSF14, and oncostatin M-which correlated with disease severity and increased bacterial products in plasma. Single-cell transcriptomics revealed a lack of type I IFNs, reduced HLA-DR in the myeloid cells of patients with severe COVID-19, and transient expression of IFN-stimulated genes. This was consistent with bulk PBMC transcriptomics and transient, low IFN-α levels in plasma during infection. These results reveal mechanisms and potential therapeutic targets for COVID-19.

Discriminating mild from critical COVID-19 by innate and adaptive immune single-cell profiling of bronchoalveolar lavages

Cell (IF: 38.62), Aug 2020, Jonas Schulte-Schrepping et al. DOI: 10.1016/j.cell.2020.08.001PubMed: 32810438
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Coronavirus disease 2019 (COVID-19) is a mild to moderate respiratory tract infection, however, a subset of patients progress to severe disease and respiratory failure. The mechanism of protective immunity in mild forms and the pathogenesis of severe COVID-19 associated with increased neutrophil counts and dysregulated immune responses remain unclear. In a dual-center, two-cohort study, we combined single-cell RNA-sequencing and single-cell proteomics of whole-blood and peripheral-blood mononuclear cells to determine changes in immune cell composition and activation in mild versus severe COVID-19 (242 samples from 109 individuals) over time. HLA-DRhiCD11chi inflammatory monocytes with an interferon-stimulated gene signature were elevated in mild COVID-19. Severe COVID-19 was marked by occurrence of neutrophil precursors, as evidence of emergency myelopoiesis, dysfunctional mature neutrophils, and HLA-DRlo monocytes. Our study provides detailed insights into the systemic immune response to SARS-CoV-2 infection and reveals profound alterations in the myeloid cell compartment associated with severe COVID-19.

CCR5 inhibition in critical COVID-19 patients decreases inflammatory cytokines, increases CD8 T-cells, and decreases SARS-CoV2 RNA in plasma by day 14

Cell (IF: 38.62), Aug 2020, Aymeric Silvin et al. DOI: 10.1016/j.cell.2020.08.002PubMed: 32810439
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Blood myeloid cells are known to be dysregulated in coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2. It is unknown whether the innate myeloid response differs with disease severity and whether markers of innate immunity discriminate high-risk patients. Thus, we performed high-dimensional flow cytometry and single-cell RNA sequencing of COVID-19 patient peripheral blood cells and detected disappearance of non-classical CD14LowCD16High monocytes, accumulation of HLA-DRLow classical monocytes (Human Leukocyte Antigen - DR isotype), and release of massive amounts of calprotectin (S100A8/S100A9) in severe cases. Immature CD10LowCD101-CXCR4+/- neutrophils with an immunosuppressive profile accumulated in the blood and lungs, suggesting emergency myelopoiesis. Finally, we show that calprotectin plasma level and a routine flow cytometry assay detecting decreased frequencies of non-classical monocytes could discriminate patients who develop a severe form of COVID-19, suggesting a predictive value that deserves prospective evaluation.

Lung transplantation for patients with severe COVID-19

Cell (IF: 38.62), Oct 2020, Benjamin J Meckiff et al. DOI: 10.1016/j.cell.2020.10.001PubMed: 33096020
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

The contribution of CD4+ T cells to protective or pathogenic immune responses to SARS-CoV-2 infection remains unknown. Here, we present single-cell transcriptomic analysis of >100,000 viral antigen-reactive CD4+ T cells from 40 COVID-19 patients. In hospitalized patients compared to non-hospitalized patients, we found increased proportions of cytotoxic follicular helper cells and cytotoxic T helper (TH) cells (CD4-CTLs) responding to SARS-CoV-2 and reduced proportion of SARS-CoV-2-reactive regulatory T cells (TREG). Importantly, in hospitalized COVID-19 patients, a strong cytotoxic TFH response was observed early in the illness, which correlated negatively with antibody levels to SARS-CoV-2 spike protein. Polyfunctional TH1 and TH17 cell subsets were underrepresented in the repertoire of SARS-CoV-2-reactive CD4+ T cells compared to influenza-reactive CD4+ T cells. Together, our analyses provide insights into the gene expression patterns of SARS-CoV-2-reactive CD4+ T cells in distinct disease severities.

Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumab-responding cytokine storm

Cell (IF: 38.62), May 2020, Yunlong Cao et al. DOI: 10.1016/j.cell.2020.05.025PubMed: 32425270
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

The COVID-19 pandemic urgently needs therapeutic and prophylactic interventions. Here, we report the rapid identification of SARS-CoV-2-neutralizing antibodies by high-throughput single-cell RNA and VDJ sequencing of antigen-enriched B cells from 60 convalescent patients. From 8,558 antigen-binding IgG1+ clonotypes, 14 potent neutralizing antibodies were identified, with the most potent one, BD-368-2, exhibiting an IC50 of 1.2 and 15 ng/mL against pseudotyped and authentic SARS-CoV-2, respectively. BD-368-2 also displayed strong therapeutic and prophylactic efficacy in SARS-CoV-2-infected hACE2-transgenic mice. Additionally, the 3.8 Å cryo-EM structure of a neutralizing antibody in complex with the spike-ectodomain trimer revealed the antibody's epitope overlaps with the ACE2 binding site. Moreover, we demonstrated that SARS-CoV-2-neutralizing antibodies could be directly selected based on similarities of their predicted CDR3H structures to those of SARS-CoV-neutralizing antibodies. Altogether, we showed that human neutralizing antibodies could be efficiently discovered by high-throughput single B cell sequencing in response to pandemic infectious diseases.

Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans

Immunity (IF: 25.73), Nov 2020, Andrew P Ferretti et al. DOI: 10.1016/j.immuni.2020.10.006PubMed: 33128877
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

Developing effective strategies to prevent or treat coronavirus disease 2019 (COVID-19) requires understanding the natural immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We used an unbiased, genome-wide screening technology to determine the precise peptide sequences in SARS-CoV-2 that are recognized by the memory CD8+ T cells of COVID-19 patients. In total, we identified 3-8 epitopes for each of the 6 most prevalent human leukocyte antigen (HLA) types. These epitopes were broadly shared across patients and located in regions of the virus that are not subject to mutational variation. Notably, only 3 of the 29 shared epitopes were located in the spike protein, whereas most epitopes were located in ORF1ab or the nucleocapsid protein. We also found that CD8+ T cells generally do not cross-react with epitopes in the four seasonal coronaviruses that cause the common cold. Overall, these findings can inform development of next-generation vaccines that better recapitulate natural CD8+ T cell immunity to SARS-CoV-2.

A human circulating immune cell landscape in aging and COVID-19

Immunity (IF: 25.73), Dec 2020, Petra Bacher et al. DOI: 10.1016/j.immuni.2020.11.016PubMed: 33296686
Single Cell Immune Profiling, Human, Immunology, Infectious Disease.

Abstract

CD4+ T cells reactive against SARS-CoV-2 can be found in unexposed individuals, and these are suggested to arise in response to common cold coronavirus (CCCoV) infection. Here, we utilized SARS-CoV-2-reactive CD4+ T cell enrichment to examine the antigen avidity and clonality of these cells, as well as the relative contribution of CCCoV cross-reactivity. SARS-CoV-2-reactive CD4+ memory T cells were present in virtually all unexposed individuals examined, displaying low functional avidity and multiple, highly variable cross-reactivities that were not restricted to CCCoVs. SARS-CoV-2-reactive CD4+ T cells from COVID-19 patients lacked cross-reactivity to CCCoVs, irrespective of strong memory T cell responses against CCCoV in all donors analyzed. In severe but not mild COVID-19, SARS-CoV-2-specific T cells displayed low functional avidity and clonality, despite increased frequencies. Our findings identify low-avidity CD4+ T cell responses as a hallmark of severe COVID-19 and argue against a protective role for CCCoV-reactive T cells in SARS-CoV-2 infection.

Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe from Mild COVID-19

Nature Immunology (IF: 22.3), Aug 2020, Ji-Yuan Zhang et al. DOI: 10.1038/s41590-020-0762PubMed: 32788748
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

In coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the relationship between disease severity and the host immune response is not fully understood. Here we performed single-cell RNA sequencing in peripheral blood samples of 5 healthy donors and 13 patients with COVID-19, including moderate, severe and convalescent cases. Through determining the transcriptional profiles of immune cells, coupled with assembled T cell receptor and B cell receptor sequences, we analyzed the functional properties of immune cells. Most cell types in patients with COVID-19 showed a strong interferon-α response and an overall acute inflammatory response. Moreover, intensive expansion of highly cytotoxic effector T cell subsets, such as CD4+ effector-GNLY (granulysin), CD8+ effector-GNLY and NKT CD160, was associated with convalescence in moderate patients. In severe patients, the immune landscape featured a deranged interferon response, profound immune exhaustion with skewed T cell receptor repertoire and broad T cell expansion. These findings illustrate the dynamic nature of immune responses during disease progression.

Multi-Omics Resolves a Sharp Disease-State Shift between Mild and Moderate COVID-19

Nature Immunology (IF: 22.3), Dec 2020, Matthew C Woodruff et al. DOI: 10.1038/s41590-020-00814
PubMed: 33028979
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

A wide spectrum of clinical manifestations has become a hallmark of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) COVID-19 pandemic, although the immunological underpinnings of diverse disease outcomes remain to be defined. We performed detailed characterization of B cell responses through high-dimensional flow cytometry to reveal substantial heterogeneity in both effector and immature populations. More notably, critically ill patients displayed hallmarks of extrafollicular B cell activation and shared B cell repertoire features previously described in autoimmune settings. Extrafollicular activation correlated strongly with large antibody-secreting cell expansion and early production of high concentrations of SARS-CoV-2-specific neutralizing antibodies. Yet, these patients had severe disease with elevated inflammatory biomarkers, multiorgan failure and death. Overall, these findings strongly suggest a pathogenic role for immune activation in subsets of patients with COVID-19. Our study provides further evidence that targeted immunomodulatory therapy may be beneficial in specific patient subpopulations and can be informed by careful immune profiling.

Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia

Science Advances (IF: 14.09), Dec 2020, Philip A Mudd et al. DOI: 10.1126/sciadv.abe3024PubMed: 33187979
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

We pursued a study of immune responses in coronavirus disease 2019 (COVID-19) and influenza patients. Compared to patients with influenza, patients with COVID-19 exhibited largely equivalent lymphocyte counts, fewer monocytes, and lower surface human leukocyte antigen (HLA)-class II expression on selected monocyte populations. Furthermore, decreased HLA-DR on intermediate monocytes predicted severe COVID-19 disease. In contrast to prevailing assumptions, very few (7 of 168) patients with COVID-19 exhibited cytokine profiles indicative of cytokine storm syndrome. After controlling for multiple factors including age and sample time point, patients with COVID-19 exhibited lower cytokine levels than patients with influenza. Up-regulation of IL-6, G-CSF, IL-1RA, and MCP1 predicted death in patients with COVID-19 but were not statistically higher than patients with influenza. Single-cell transcriptional profiling revealed profound suppression of interferon signaling among patients with COVID-19. When considered across the spectrum of peripheral immune profiles, patients with COVID-19 are less inflamed than patients with influenza.

Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells

Nature Communications (IF: 13.61), Aug 2020, Chuang Guo et al. DOI: 10.1038/s41467-020-17834
PubMed: 32764665
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Several studies show that the immunosuppressive drugs targeting the interleukin-6 (IL-6) receptor, including tocilizumab, ameliorate lethal inflammatory responses in COVID-19 patients infected with SARS-CoV-2. Here, by employing single-cell analysis of the immune cell composition of two severe-stage COVID-19 patients prior to and following tocilizumab-induced remission, we identify a monocyte subpopulation that contributes to the inflammatory cytokine storms. Furthermore, although tocilizumab treatment attenuates the inflammation, immune cells, including plasma B cells and CD8+ T cells, still exhibit robust humoral and cellular antiviral immune responses. Thus, in addition to providing a high-dimensional dataset on the immune cell distribution at multiple stages of the COVID-19, our work also provides insights into the therapeutic effects of tocilizumab, and identifies potential target cell populations for treating COVID-19-related cytokine storms.

Influenza virus infection increases ACE2 expression and shedding in human small airway epithelial cells

Science Immunology (IF: 13.41), Jan 2021, Anthony Kusnadi et al. DOI: 10.1126/sciimmunol.abe4782
PubMed: 33478949
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

The molecular properties of CD8+ T cells that respond to SARS-CoV-2 infection are not fully known. Here, we report on the single-cell transcriptomes of >80,000 virus-reactive CD8+ T cells, obtained using a modified Antigen-Reactive T cell Enrichment (ARTE) assay, from 39 COVID-19 patients and 10 healthy subjects. COVID-19 patients segregated into two groups based on whether the dominant CD8+ T cell response to SARS-CoV-2 was 'exhausted' or not. SARS-CoV-2-reactive cells in the exhausted subset were increased in frequency and displayed lesser cytotoxicity and inflammatory features in COVID-19 patients with mild compared to severe illness. In contrast, SARS-CoV-2-reactive cells in the dominant non-exhausted subset from patients with severe disease showed enrichment of transcripts linked to co-stimulation, pro-survival NF-κB signaling, and anti-apoptotic pathways, suggesting the generation of robust CD8+ T cell memory responses in patients with severe COVID-19 illness. CD8+ T cells reactive to influenza and respiratory syncytial virus from healthy subjects displayed polyfunctional features and enhanced glycolysis. Cells with such features were largely absent in SARS-CoV-2-reactive cells from both COVID-19 patients and healthy controls non-exposed to SARS-CoV-2. Overall, our single-cell analysis revealed substantial diversity in the nature of CD8+ T cells responding to SARS-CoV-2.

Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques

Science Immunology (IF: 13.41), Jul 2020, Jeong Seok Lee et al. DOI: 10.1126/sciimmunol.abd1554
PubMed: 32651212
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Although most SARS-CoV-2-infected individuals experience mild coronavirus disease 2019 (COVID-19), some patients suffer from severe COVID-19, which is accompanied by acute respiratory distress syndrome and systemic inflammation. To identify factors driving severe progression of COVID-19, we performed single-cell RNA-seq using peripheral blood mononuclear cells (PBMCs) obtained from healthy donors, patients with mild or severe COVID-19, and patients with severe influenza. Patients with COVID-19 exhibited hyper-inflammatory signatures across all types of cells among PBMCs, particularly up-regulation of the TNF/IL-1β-driven inflammatory response as compared to severe influenza. In classical monocytes from patients with severe COVID-19, type I IFN response co-existed with the TNF/IL-1β-driven inflammation, and this was not seen in patients with milder COVID-19. Interestingly, we documented type I IFN-driven inflammatory features in patients with severe influenza as well. Based on this, we propose that the type I IFN response plays a pivotal role in exacerbating inflammation in severe COVID-19.

Progenitor identification and SARS-CoV-2 infection in human distal lung organoids

Signal Transduction and Targeted Therapy (IF: 13.2), Aug 2020, Fan Zhang et al. DOI: 10.1038/s41392-020-00263PubMed: 32796814
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

The global Coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has affected more than eight million people. There is an urgent need to investigate how the adaptive immunity is established in COVID-19 patients. In this study, we profiled adaptive immune cells of PBMCs from recovered COVID-19 patients with varying disease severity using single-cell RNA and TCR/BCR V(D)J sequencing. The sequencing data revealed SARS-CoV-2-specific shuffling of adaptive immune repertories and COVID-19-induced remodeling of peripheral lymphocytes. Characterization of variations in the peripheral T and B cells from the COVID-19 patients revealed a positive correlation of humoral immune response and T-cell immune memory with disease severity. Sequencing and functional data revealed SARS-CoV-2-specific T-cell immune memory in the convalescent COVID-19 patients. Furthermore, we also identified novel antigens that are responsive in the convalescent patients. Altogether, our study reveals adaptive immune repertories underlying pathogenesis and recovery in severe versus mild COVID-19 patients, providing valuable information for potential vaccine and therapeutic development against SARS-CoV-2 infection.

Distinct inflammatory profiles distinguish COVID-19 from influenza with limited contributions from cytokine storm

Cell (IF: 38.62), May 2020, Pierre Bost et al. DOI: 10.1016/j.cell.2020.05.006PubMed: 32479746
Single Cell Gene Expression, Human, Computational Method, Infectious Disease.

Abstract

Viruses are a constant threat to global health as highlighted by the current COVID-19 pandemic. Currently, lack of data underlying how the human host interacts with viruses, including the SARS-CoV-2 virus, limits effective therapeutic intervention. We introduce Viral-Track, a computational method that globally scans unmapped single-cell RNA sequencing (scRNA-seq) data for the presence of viral RNA, enabling transcriptional cell sorting of infected versus bystander cells. We demonstrate the sensitivity and specificity of Viral-Track to systematically detect viruses from multiple models of infection, including hepatitis B virus, in an unsupervised manner. Applying Viral-Track to bronchoalveloar-lavage samples from severe and mild COVID-19 patients reveals a dramatic impact of the virus on the immune system of severe patients compared to mild cases. Viral-Track detects an unexpected co-infection of the human metapneumovirus, present mainly in monocytes perturbed in type-I interferon (IFN)-signaling. Viral-Track provides a robust technology for dissecting the mechanisms of viral-infection and pathology.

A Shift Towards an Immature Myeloid Profile in Peripheral Blood of Critically Ill COVID-19 Patients

Science Translational Medicine (IF: 18.56), Dec 2020, Ankit Bharat et al. DOI: 10.1126/scitranslmed.abe4282
PubMed: 33257409
Single Cell Gene Expression, Human, Immunology, Infectious Disease.

Abstract

Lung transplantation can potentially be a life-saving treatment for patients with nonresolving COVID-19-associated respiratory failure. Concerns limiting lung transplantation include recurrence of SARS-CoV-2 infection in the allograft, technical challenges imposed by viral-mediated injury to the native lung, and the potential risk for allograft infection by pathogens causing ventilator-associated pneumonia in the native lung. Additionally, the native lung might recover, resulting in long-term outcomes preferable to those of transplant. Here, we report the results of lung transplantation in three patients with nonresolving COVID-19-associated respiratory failure. We performed single-molecule fluorescence in situ hybridization (smFISH) to detect both positive and negative strands of SARS-CoV-2 RNA in explanted lung tissue from the three patients and in additional control lung tissue samples. We conducted extracellular matrix imaging and single-cell RNA sequencing on explanted lung tissue from the three patients who underwent transplantation and on warm postmortem lung biopsies from two patients who had died from COVID-19-associated pneumonia. Lungs from these five patients with prolonged COVID-19 disease were free of SARS-CoV-2 as detected by smFISH, but pathology showed extensive evidence of injury and fibrosis that resembled end-stage pulmonary fibrosis. Our findings suggest that some patients with severe COVID-19 develop fibrotic lung disease for which lung transplantation is their only option for survival.

Hypertension delays viral clearance and exacerbates airway hyperinflammation in patients with COVID-19

Cell Stem Cell (IF: 23.45), Dec 2020, Arunima Purkayastha et al. DOI: 10.1016/j.stem.2020.11.010
PubMed: 33259798
Single Cell Gene Expression, Human, Developmental Biology, Infectious Disease.

Abstract

Current smoking is associated with increased risk of severe COVID-19, but it is not clear how cigarette smoke (CS) exposure affects SARS-CoV-2 airway cell infection. We directly exposed air-liquid interface (ALI) cultures derived from primary human nonsmoker airway basal stem cells (ABSCs) to short term CS and then infected them with SARS-CoV-2. We found an increase in the number of infected airway cells after CS exposure with a lack of ABSC proliferation. Single-cell profiling of the cultures showed that the normal interferon response was reduced after CS exposure with infection. Treatment of CS-exposed ALI cultures with interferon β-1 abrogated the viral infection, suggesting one potential mechanism for more severe viral infection. Our data show that acute CS exposure allows for more severe airway epithelial disease from SARS-CoV-2 by reducing the innate immune response and ABSC proliferation and has implications for disease spread and severity in people exposed to CS.

Androgen Signaling Regulates SARS-CoV-2 Receptor Levels and Is Associated with Severe COVID-19 Symptoms in Men

Science Translational Medicine (IF: 18.56), Jan 2021, Emily Speranza et al. DOI: 10.1126/scitranslmed.abe8146
PubMed: 33431511
Single Cell Gene Expression, Primate, Infectious Disease.

Abstract

Detailed knowledge about the dynamics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is important for uncovering the viral and host factors that contribute to coronavirus disease 2019 (COVID-19) pathogenesis. Old-World nonhuman primates recapitulate mild to moderate cases of COVID-19, thereby serving as important pathogenesis models. We compared African green monkeys inoculated with infectious SARS-CoV-2 or irradiated, inactivated virus to study the dynamics of virus replication throughout the respiratory tract. Genomic RNA from the animals inoculated with the irradiated virus was found to be highly stable, whereas subgenomic RNA, an indicator of viral replication, was found to degrade quickly. We combined this information with single-cell RNA sequencing of cells isolated from the lung and lung-draining mediastinal lymph nodes and developed new analysis methods for unbiased targeting of important cells in the host response to SARS-CoV-2 infection. Through detection of reads to the viral genome, we were able to determine that replication of the virus in the lungs appeared to occur mainly in pneumocytes, whereas macrophages drove the inflammatory response. Monocyte-derived macrophages recruited to the lungs, rather than tissue-resident alveolar macrophages, were most likely to be responsible for phagocytosis of infected cells and cellular debris early in infection, with their roles switching during clearance of infection. Together, our dataset provides a detailed view of the dynamics of virus replication and host responses over the course of mild COVID-19 and serves as a valuable resource to identify therapeutic targets.

Imbalance of Regulatory and Cytotoxic SARS-CoV-2-Reactive CD4+ T Cells in COVID-19

American Journal of Respiratory and Critical Care Medicine (IF: 15.3), May 2020, Haijun Zhang et al. DOI: 10.1164/rccm.202003-0541OCPubMed: 32432483
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Rationale: Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease (COVID-19), a predominantly respiratory illness. The first step in SARS-CoV-2 infection is binding of the virus to ACE2 (angiotensin-converting enzyme 2) on the airway epithelium.Objectives: The objective was to gain insight into the expression of ACE2 in the human airway epithelium.Methods: Airway epithelia sampled by fiberoptic bronchoscopy of trachea, large airway epithelia (LAE), and small airway epithelia (SAE) of nonsmokers and smokers were analyzed for expression of ACE2 and other coronavirus infection-related genes using microarray, RNA sequencing, and 10x single-cell transcriptome analysis, with associated examination of ACE2-related microRNA.Measurements and Main Results: 1) ACE2 is expressed similarly in the trachea and LAE, with lower expression in the SAE; 2) in the SAE, ACE2 is expressed in basal, intermediate, club, mucus, and ciliated cells; 3) ACE2 is upregulated in the SAE by smoking, significantly in men; 4) levels of miR-1246 expression could play a role in ACE2 upregulation in the SAE of smokers; and 5) ACE2 is expressed in airway epithelium differentiated in vitro on air-liquid interface cultures from primary airway basal stem/progenitor cells; this can be replicated using LAE and SAE immortalized basal cell lines derived from healthy nonsmokers.Conclusions: ACE2, the gene encoding the receptor for SARS-CoV-2, is expressed in the human airway epithelium, with variations in expression relevant to the biology of initial steps in SARS-CoV-2 infection.

Single-cell RNA sequencing reveals SARS-CoV-2 infection dynamics in lungs of African green monkeys

Nature Communications (IF: 13.61), Oct 2020, Satria P Sajuthi et al. DOI: 10.1038/s41467-020-18781-2 PubMed: 33046696
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, an emerging virus that utilizes host proteins ACE2 and TMPRSS2 as entry factors. Understanding the factors affecting the pattern and levels of expression of these genes is important for deeper understanding of SARS-CoV-2 tropism and pathogenesis. Here we explore the role of genetics and co-expression networks in regulating these genes in the airway, through the analysis of nasal airway transcriptome data from 695 children. We identify expression quantitative trait loci for both ACE2 and TMPRSS2, that vary in frequency across world populations. We find TMPRSS2 is part of a mucus secretory network, highly upregulated by type 2 (T2) inflammation through the action of interleukin-13, and that the interferon response to respiratory viruses highly upregulates ACE2 expression. IL-13 and virus infection mediated effects on ACE2 expression were also observed at the protein level in the airway epithelium. Finally, we define airway responses to common coronavirus infections in children, finding that these infections generate host responses similar to other viral species, including upregulation of IL6 and ACE2. Our results reveal possible mechanisms influencing SARS-CoV-2 infectivity and COVID-19 clinical outcomes.

Age-determined expression of priming protease TMPRSS2 and localization of SARS-CoV-2 in lung epithelium

European Respiratory Journal (IF: 11.71), Jan 2021, Kelly S Schweitzer et al. DOI: 10.1183/13993003.03988-2020PubMed: 33419885

Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Patients with COVID-19 caused by severe acute respiratory syndrome coronavirus (SARS-Co-V)-2 demonstrate high rates of co-infection with respiratory viruses, including influenza A (IAV), suggesting pathogenic interactions. We investigated how IAV may increase the risk for COVID-19 lung disease, focusing on the receptor Angiotensin Convertase Enzyme 2 (ACE2) and the protease TMPRSS2, which cooperate to uptake SARS-CoV-2 intracellular. We found, using single cell RNA sequencing of distal human non-diseased lung homogenates, that at baseline, ACE2 is minimally expressed in basal, goblet, ciliated, and secretory epithelial cells populating small airways. We focused on human small airway epithelial cells (SAEC), central to the pathogenesis of lung injury following viral infections. Primary SAEC from non-diseased donor lungs apically infected (at air-liquid interface) with IAV (up to 3×105 pfu; ~1 MOI) markedly (8-fold) boosted the expression of ACE2, paralleling that of STAT1, a transcription factor activated by viruses. IAV increased the apparent electrophoretic mobility of intracellular ACE2 and generated an ACE2 fragment (90 kDa) in apical secretions, suggesting cleavage of this receptor. IAV also increased the expression of two proteases known to cleave ACE2, sheddase ADAM17 (TACE) and TMPRSS2 and increased the TMPRSS2 zymogen and its mature fragments, implicating proteolytic autoactivation. These results indicate that IAV amplifies the expression of molecules necessary for SARS-CoV-2 infection of the distal lung. Further, posttranslational changes in ACE2 by IAV may increase the vulnerability to lung injury such as ARDS during viral co-infections. These findings support prevention and treatment efforts of influenza infections during the COVID-19 pandemic.

Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19

Nature Biotechnology (IF: 42.3), Jun 2020, Robert Lorenz Chua et al. DOI: 10.1038/s41587-020-0602-4
PubMed: 32591762
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

To investigate the immune response and mechanisms associated with severe coronavirus disease 2019 (COVID-19), we performed single-cell RNA sequencing on nasopharyngeal and bronchial samples from 19 clinically well-characterized patients with moderate or critical disease and from five healthy controls. We identified airway epithelial cell types and states vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In patients with COVID-19, epithelial cells showed an average three-fold increase in expression of the SARS-CoV-2 entry receptor ACE2, which correlated with interferon signals by immune cells. Compared to moderate cases, critical cases exhibited stronger interactions between epithelial and immune cells, as indicated by ligand-receptor expression profiles, and activated immune cells, including inflammatory macrophages expressing CCL2, CCL3, CCL20, CXCL1, CXCL3, CXCL10, IL8, IL1B and TNF. The transcriptional differences in critical cases compared to moderate cases likely contribute to clinical observations of heightened inflammatory tissue damage, lung injury and respiratory failure.

Unbiased Screens Show CD8+ T Cells of COVID-19 Patients Recognize Shared Epitopes in SARS-CoV-2 that Largely Reside outside the Spike Protein

Cell (IF: 38.62), Jan 2021, Timothy N Hoang et al. DOI: 10.1016/j.cell.2020.11.007PubMed: 33278358
Single Cell Immune Profiling, Primate, Infectious Disease.

Abstract

SARS-CoV-2-induced hypercytokinemia and inflammation are critically associated with COVID-19 severity. Baricitinib, a clinically approved JAK1/JAK2 inhibitor, is currently being investigated in COVID-19 clinical trials. Here, we investigated the immunologic and virologic efficacy of baricitinib in a rhesus macaque model of SARS-CoV-2 infection. Viral shedding measured from nasal and throat swabs, bronchoalveolar lavages, and tissues was not reduced with baricitinib. Type I interferon (IFN) antiviral responses and SARS-CoV-2-specific T cell responses remained similar between the two groups. Animals treated with baricitinib showed reduced inflammation, decreased lung infiltration of inflammatory cells, reduced NETosis activity, and more limited lung pathology. Importantly, baricitinib-treated animals had a rapid and remarkably potent suppression of lung macrophage production of cytokines and chemokines responsible for inflammation and neutrophil recruitment. These data support a beneficial role for, and elucidate the immunological mechanisms underlying, the use of baricitinib as a frontline treatment for inflammation induced by SARS-CoV-2 infection.

Single-cell analysis reveals bronchoalveolar epithelial dysfunction in COVID-19 patients

Nature Medicine (IF: 36.23), May 2020, Mingfeng Liao et al. DOI: 10.1038/s41591-020-0901-9PubMed: 32398875
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

Respiratory immune characteristics associated with Coronavirus Disease 2019 (COVID-19) severity are currently unclear. We characterized bronchoalveolar lavage fluid immune cells from patients with varying severity of COVID-19 and from healthy people by using single-cell RNA sequencing. Proinflammatory monocyte-derived macrophages were abundant in the bronchoalveolar lavage fluid from patients with severe COVID-9. Moderate cases were characterized by the presence of highly clonally expanded CD8+ T cells. This atlas of the bronchoalveolar immune microenvironment suggests potential mechanisms underlying pathogenesis and recovery in COVID-19.

Transplantation of ACE2- Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia

Cell Research (IF: 20.4), Jan 2021, Els Wauters et al. DOI: 10.1038/s41422-020-00455-9PubMed: 33473155
Single Cell Immune Profiling, Human, Infectious Disease.

Abstract

How the innate and adaptive host immune system miscommunicate to worsen COVID-19 immunopathology has not been fully elucidated. Here, we perform single-cell deep-immune profiling of bronchoalveolar lavage (BAL) samples from 5 patients with mild and 26 with critical COVID-19 in comparison to BALs from non-COVID-19 pneumonia and normal lung. We use pseudotime inference to build T-cell and monocyte-to-macrophage trajectories and model gene expression changes along them. In mild COVID-19, CD8+ resident-memory (TRM) and CD4+ T-helper-17 (TH17) cells undergo active (presumably antigen-driven) expansion towards the end of the trajectory, and are characterized by good effector functions, while in critical COVID-19 they remain more naïve. Vice versa, CD4+ T-cells with T-helper-1 characteristics (TH1-like) and CD8+ T-cells expressing exhaustion markers (TEX-like) are enriched halfway their trajectories in mild COVID-19, where they also exhibit good effector functions, while in critical COVID-19 they show evidence of inflammation-associated stress at the end of their trajectories. Monocyte-to-macrophage trajectories show that chronic hyperinflammatory monocytes are enriched in critical COVID-19, while alveolar macrophages, otherwise characterized by anti-inflammatory and antigen-presenting characteristics, are depleted. In critical COVID-19, monocytes contribute to an ATP-purinergic signaling-inflammasome footprint that could enable COVID-19 associated fibrosis and worsen disease-severity. Finally, viral RNA-tracking reveals infected lung epithelial cells, and a significant proportion of neutrophils and macrophages that are involved in viral clearance.

COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis

Nature (IF: 46.49), Nov 2020, Ameen A Salahudeen et al. DOI: 10.1038/s41586-020-3014-1PubMed: 33238290
Single Cell Gene Expression, Human, Developmental Biology, Infectious Disease.

Abstract

The distal lung contains terminal bronchioles and alveoli that facilitate gas exchange. Three-dimensional in vitro human distal lung culture systems would strongly facilitate the investigation of pathologies such as interstitial lung disease, cancer and coronavirus disease 2019 (COVID-19) pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Here we describe the development of a long-term feeder-free, chemically defined culture system for distal lung progenitors as organoids derived from single adult human alveolar epithelial type II (AT2) or KRT5+ basal cells. AT2 organoids were able to differentiate into AT1 cells, and basal cell organoids developed lumens lined with differentiated club and ciliated cells. Single-cell analysis of KRT5+ cells in basal organoids revealed a distinct population of ITGA6+ITGB4+ mitotic cells, whose offspring further segregated into a TNFRSF12Ahi subfraction that comprised about ten per cent of KRT5+ basal cells. This subpopulation formed clusters within terminal bronchioles and exhibited enriched clonogenic organoid growth activity. We created distal lung organoids with apical-out polarity to present ACE2 on the exposed external surface, facilitating infection of AT2 and basal cultures with SARS-CoV-2 and identifying club cells as a target population. This long-term, feeder-free culture of human distal lung organoids, coupled with single-cell analysis, identifies functional heterogeneity among basal cells and establishes a facile in vitro organoid model of human distal lung infections, including COVID-19-associated pneumonia.

Multi-clonal SARS-CoV-2 neutralization by antibodies isolated from severe COVID-19 convalescent donors

Cell Stem Cell (IF: 23.45), Dec 2020, Ryan M Samuel et al. DOI: 10.1016/j.stem.2020.11.009PubMed: 33232663
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

SARS-CoV-2 infection has led to a global health crisis, and yet our understanding of the disease and potential treatment options remains limited. The infection occurs through binding of the virus with angiotensin converting enzyme 2 (ACE2) on the cell membrane. Here, we established a screening strategy to identify drugs that reduce ACE2 levels in human embryonic stem cell (hESC)-derived cardiac cells and lung organoids. Target analysis of hit compounds revealed androgen signaling as a key modulator of ACE2 levels. Treatment with antiandrogenic drugs reduced ACE2 expression and protected hESC-derived lung organoids against SARS-CoV-2 infection. Finally, clinical data on COVID-19 patients demonstrated that prostate diseases, which are linked to elevated androgen, are significant risk factors and that genetic variants that increase androgen levels are associated with higher disease severity. These findings offer insights on the mechanism of disproportionate disease susceptibility in men and identify antiandrogenic drugs as candidate therapeutics for COVID-19.

Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19

Cell Metabolism (IF: 24.29), Dec 2020, Katie C Coate et al. DOI: 10.1016/j.cmet.2020.11.006PubMed: 33207245
Single Cell Gene Expression, Human, Immunology, Infectious Disease.

Abstract

Isolated reports of new-onset diabetes in individuals with COVID-19 have led to the hypothesis that SARS-CoV-2 is directly cytotoxic to pancreatic islet β cells. This would require binding and entry of SARS-CoV-2 into β cells via co-expression of its canonical cell entry factors, angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2); however, their expression in human pancreas has not been clearly defined. We analyzed six transcriptional datasets of primary human islet cells and found that ACE2 and TMPRSS2 were not co-expressed in single β cells. In pancreatic sections, ACE2 and TMPRSS2 protein was not detected in β cells from donors with and without diabetes. Instead, ACE2 protein was expressed in islet and exocrine tissue microvasculature and in a subset of pancreatic ducts, whereas TMPRSS2 protein was restricted to ductal cells. These findings reduce the likelihood that SARS-CoV-2 directly infects β cells in vivo through ACE2 and TMPRSS2.

Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19

Cell Stem Cell (IF: 23.45), Jun 2020, Liuliu Yang et al. DOI: 10.1016/j.stem.2020.06.015PubMed: 32579880
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

SARS-CoV-2 has caused the COVID-19 pandemic. There is an urgent need for physiological models to study SARS-CoV-2 infection using human disease-relevant cells. COVID-19 pathophysiology includes respiratory failure but involves other organ systems including gut, liver, heart, and pancreas. We present an experimental platform comprised of cell and organoid derivatives from human pluripotent stem cells (hPSCs). A Spike-enabled pseudo-entry virus infects pancreatic endocrine cells, liver organoids, cardiomyocytes, and dopaminergic neurons. Recent clinical studies show a strong association with COVID-19 and diabetes. We find that human pancreatic beta cells and liver organoids are highly permissive to SARS-CoV-2 infection, further validated using adult primary human islets and adult hepatocyte and cholangiocyte organoids. SARS-CoV-2 infection caused striking expression of chemokines, as also seen in primary human COVID-19 pulmonary autopsy samples. hPSC-derived cells/organoids provide valuable models for understanding the cellular responses of human tissues to SARS-CoV-2 infection and for disease modeling of COVID-19.

Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients

Nature Medicine (IF: 36.23), May 2020, Waradon Sungnak et al. DOI: 10.1038/s41591-020-0868-6
PubMed: 32327758
Single Cell Gene Expression, Human, Cell Atlas, Infectious Disease.

Abstract

We investigated SARS-CoV-2 potential tropism by surveying expression of viral entry-associated genes in single-cell RNA-sequencing data from multiple tissues from healthy human donors. We co-detected these transcripts in specific respiratory, corneal and intestinal epithelial cells, potentially explaining the high efficiency of SARS-CoV-2 transmission. These genes are co-expressed in nasal epithelial cells with genes involved in innate immunity, highlighting the cells' potential role in initial viral infection, spread and clearance. The study offers a useful resource for further lines of inquiry with valuable clinical samples from COVID-19 patients and we provide our data in a comprehensive, open and user-friendly fashion at www.covid19cellatlas.org.

Neurological Manifestations of COVID-19 Feature T Cell Exhaustion and Dedifferentiated Monocytes in Cerebrospinal Fluid

Nature Biotechnology (IF: 42.3), Dec 2020, Saskia Trump et al. DOI: 10.1038/s41587-020-00796-1
PubMed: 33361824
Single Cell Gene Expression, Human, Infectious Disease.

Abstract

In coronavirus disease 2019 (COVID-19), hypertension and cardiovascular diseases are major risk factors for critical disease progression. However, the underlying causes and the effects of the main anti-hypertensive therapies-angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)-remain unclear. Combining clinical data (n = 144) and single-cell sequencing data of airway samples (n = 48) with in vitro experiments, we observed a distinct inflammatory predisposition of immune cells in patients with hypertension that correlated with critical COVID-19 progression. ACEI treatment was associated with dampened COVID-19-related hyperinflammation and with increased cell intrinsic antiviral responses, whereas ARB treatment related to enhanced epithelial-immune cell interactions. Macrophages and neutrophils of patients with hypertension, in particular under ARB treatment, exhibited higher expression of the pro-inflammatory cytokines CCL3 and CCL4 and the chemokine receptor CCR1. Although the limited size of our cohort does not allow us to establish clinical efficacy, our data suggest that the clinical benefits of ACEI treatment in patients with COVID-19 who have hypertension warrant further investigation.

Cell-Type-Specific Immune Dysregulation in Severely Ill COVID-19 Patients

Cell (IF: 38.62), Oct 2020, Zharko Daniloski et al. DOI: 10.1016/j.cell.2020.10.030PubMed: 33147445
Single Cell Immune Profiling, Human, Functional Genomics, Infectious Disease.

Abstract

To better understand host-virus genetic dependencies and find potential therapeutic targets for COVID-19, we performed a genome-scale CRISPR loss-of-function screen to identify host factors required for SARS-CoV-2 viral infection of human alveolar epithelial cells. Top-ranked genes cluster into distinct pathways, including the vacuolar ATPase proton pump, Retromer, and Commander complexes. We validate these gene targets using several orthogonal methods such as CRISPR knockout, RNA interference knockdown, and small-molecule inhibitors. Using single-cell RNA-sequencing, we identify shared transcriptional changes in cholesterol biosynthesis upon loss of top-ranked genes. In addition, given the key role of the ACE2 receptor in the early stages of viral entry, we show that loss of RAB7A reduces viral entry by sequestering the ACE2 receptor inside cells. Overall, this work provides a genome-scale, quantitative resource of the impact of the loss of each host gene on fitness/response to viral infection.

Single cell RNA and immune repertoire profiling of COVID-19 patients reveal novel neutralizing antibody

Cell (IF: 38.62), May 2020, Carly G K Ziegler et al. DOI: 10.1016/j.cell.2020.04.035PubMed: 32413319
Single Cell Gene Expression, Human, Immunology, Infectious Disease.

Abstract

There is pressing urgency to understand the pathogenesis of the severe acute respiratory syndrome coronavirus clade 2 (SARS-CoV-2), which causes the disease COVID-19. SARS-CoV-2 spike (S) protein binds angiotensin-converting enzyme 2 (ACE2), and in concert with host proteases, principally transmembrane serine protease 2 (TMPRSS2), promotes cellular entry. The cell subsets targeted by SARS-CoV-2 in host tissues and the factors that regulate ACE2 expression remain unknown. Here, we leverage human, non-human primate, and mouse single-cell RNA-sequencing (scRNA-seq) datasets across health and disease to uncover putative targets of SARS-CoV-2 among tissue-resident cell subsets. We identify ACE2 and TMPRSS2 co-expressing cells within lung type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells. Strikingly, we discovered that ACE2 is a human interferon-stimulated gene (ISG) in vitro using airway epithelial cells and extend our findings to in vivo viral infections. Our data suggest that SARS-CoV-2 could exploit species-specific interferon-driven upregulation of ACE2, a tissue-protective mediator during lung injury, to enhance infection.

Single-cell landscape of immunological responses in patients with COVID-19

Immunity (IF: 25.73), Jan 2021, Michael Heming et al. DOI: 10.1016/j.immuni.2020.12.011PubMed: 33382973
Single Cell Gene Expression, Human, Infectious Disease, Neuroscience.

Abstract

Patients suffering from Coronavirus disease 2019 (COVID-19) can develop neurological sequelae, such as headache and neuroinflammatory or cerebrovascular disease. These conditions-termed here as Neuro-COVID-are more frequent in patients with severe COVID-19. To understand the etiology of these neurological sequelae, we utilized single-cell sequencing and examined the immune cell profiles from the cerebrospinal fluid (CSF) of Neuro-COVID patients compared with patients with non-inflammatory and autoimmune neurological diseases or with viral encephalitis. The CSF of Neuro-COVID patients exhibited an expansion of dedifferentiated monocytes and of exhausted CD4+ T cells. Neuro-COVID CSF leukocytes featured an enriched interferon signature; however, this was less pronounced than in viral encephalitis. Repertoire analysis revealed broad clonal T cell expansion and curtailed interferon response in severe compared with mild Neuro-COVID patients. Collectively, our findings document the CSF immune compartment in Neuro-COVID patients and suggest compromised antiviral responses in this setting.

Low-Avidity CD4+ T Cell Responses to SARS-CoV-2 in Unexposed Individuals and Humans with Severe COVID-19

Science Advances (IF: 14.09), Jul 2020, David H Brann et al. DOI: 10.1126/sciadv.abc5801PubMed: 32937591
Single Cell Gene Expression, Mouse, Infectious Disease.

Abstract

Altered olfactory function is a common symptom of COVID-19, but its etiology is unknown. A key question is whether SARS-CoV-2 (CoV-2) - the causal agent in COVID-19 - affects olfaction directly, by infecting olfactory sensory neurons or their targets in the olfactory bulb, or indirectly, through perturbation of supporting cells. Here we identify cell types in the olfactory epithelium and olfactory bulb that express SARS-CoV-2 cell entry molecules. Bulk sequencing demonstrated that mouse, non-human primate and human olfactory mucosa expresses two key genes involved in CoV-2 entry, ACE2 and TMPRSS2. However, single cell sequencing revealed that ACE2 is expressed in support cells, stem cells, and perivascular cells, rather than in neurons. Immunostaining confirmed these results and revealed pervasive expression of ACE2 protein in dorsally-located olfactory epithelial sustentacular cells and olfactory bulb pericytes in the mouse. These findings suggest that CoV-2 infection of non-neuronal cell types leads to anosmia and related disturbances in odor perception in COVID-19 patients.

Direct Exposure to SARS-CoV-2 and Cigarette Smoke Increases Infection Severity and Alters the Stem Cell-Derived Airway Repair Response

Science Immunology (IF: 13.41), May 2020, Ruochen Zang et al. DOI: 10.1126/sciimmunol.abc3582
PubMed: 32404436
Single Cell Gene Expression, Mouse, Infectious Disease.

Abstract

Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA are frequently observed in COVID-19 patients. However, it is unclear whether SARS-CoV-2 replicates in the human intestine and contributes to possible fecal-oral transmission. Here, we report productive infection of SARS-CoV-2 in ACE2+ mature enterocytes in human small intestinal enteroids. Expression of two mucosa-specific serine proteases, TMPRSS2 and TMPRSS4, facilitated SARS-CoV-2 spike fusogenic activity and promoted virus entry into host cells. We also demonstrate that viruses released into the intestinal lumen were inactivated by simulated human colonic fluid, and infectious virus was not recovered from the stool specimens of COVID-19 patients. Our results highlight the intestine as a potential site of SARS-CoV-2 replication, which may contribute to local and systemic illness and overall disease progression.

Identification of Required Host Factors for SARS-CoV-2 Infection in Human Cells

Proceedings of the National Academy of Sciences of the United States of America (IF: 10.62), Oct 2020, Lisa Miorin et al. DOI: 10.1073/pnas.2016650117PubMed: 33097660
Single Cell Immune Profiling, Primate, Infectious Disease.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic that is a serious global health problem. Evasion of IFN-mediated antiviral signaling is a common defense strategy that pathogenic viruses use to replicate and propagate in their host. In this study, we show that SARS-CoV-2 is able to efficiently block STAT1 and STAT2 nuclear translocation in order to impair transcriptional induction of IFN-stimulated genes (ISGs). Our results demonstrate that the viral accessory protein Orf6 exerts this anti-IFN activity. We found that SARS-CoV-2 Orf6 localizes at the nuclear pore complex (NPC) and directly interacts with Nup98-Rae1 via its C-terminal domain to impair docking of cargo-receptor (karyopherin/importin) complex and disrupt nuclear import. In addition, we show that a methionine-to-arginine substitution at residue 58 impairs Orf6 binding to the Nup98-Rae1 complex and abolishes its IFN antagonistic function. All together our data unravel a mechanism of viral antagonism in which a virus hijacks the Nup98-Rae1 complex to overcome the antiviral action of IFN.

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