This report focuses on Immunity and COVID19

1. **SARS-CoV-2 infection may affect primarily T lymphocytes**
2. **Hyperactivation of monocyte-derived macrophages**
3. **Replacement of tissue resident alveolar macrophages with recruited inflammatory monocytes, neutrophils, and macrophages and an altered CD8+ T cell cytotoxic response, in severe cases compared to mild cases.**
4. **Anti-inflammatory or cytokine storm inhibition – Tocilizumab, digitoxin, JAK1 inhibition, Atazanavir**
5. **LY6E impairs coronavirus fusion and confers immune control of viral disease**
6. **Monalizumab - a NKG2A inhibitor**

1. SARS-CoV-2 infection may affect primarily T lymphocytes, particularly CD4+ and CD8+ T cells, resulting in a decrease in numbers as well as IFN-γ production by CD4+ T cells. In a retrospective observational study funded by grants from Tongji Hospital for the Pilot Scheme Project and partly supported by the Chinese National Thirteenth Five Years Project in Science and Technology for Infectious Disease, Chen et al showed that the median age of severe and moderate cases was 61.0 and 52.0 years, respectively. Whilst the common clinical manifestations included fever, cough, and fatigue the severe cases demonstrated more frequent dyspnea, lymphopenia, and hypoalbuminemia, with higher levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer as well as markedly higher levels of IL-2R, IL-6, IL-10, and TNF-α. Absolute numbers of T lymphocytes, CD4+ T cells, and CD8+ T cells decreased in nearly all the patients, and were markedly lower in severe cases than moderate cases. The expression of IFN-γ by CD4+ T cells tended to be lower in severe cases than in moderate cases.

Source: Guang et al. (2020), JCI. Clinical and immunological features of severe and moderate coronavirus disease 2019.
https://www.jci.org/articles/view/137244?fbclid=IwAR0HcF1DebxTN_FfVIL-V3AJFz2xixrR4zIzsi8_xDeIHGjuyofdhnCydh0

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2. Hyperactivation of monocyte-derived macrophages. In this review published in Nature Reviews Immunology, Merad & Martin (2020) review potentially pathological roles of macrophages during SARS-CoV-2 infection and discuss ongoing and prospective therapeutic strategies to modulate macrophage activation in patients with COVID-19.

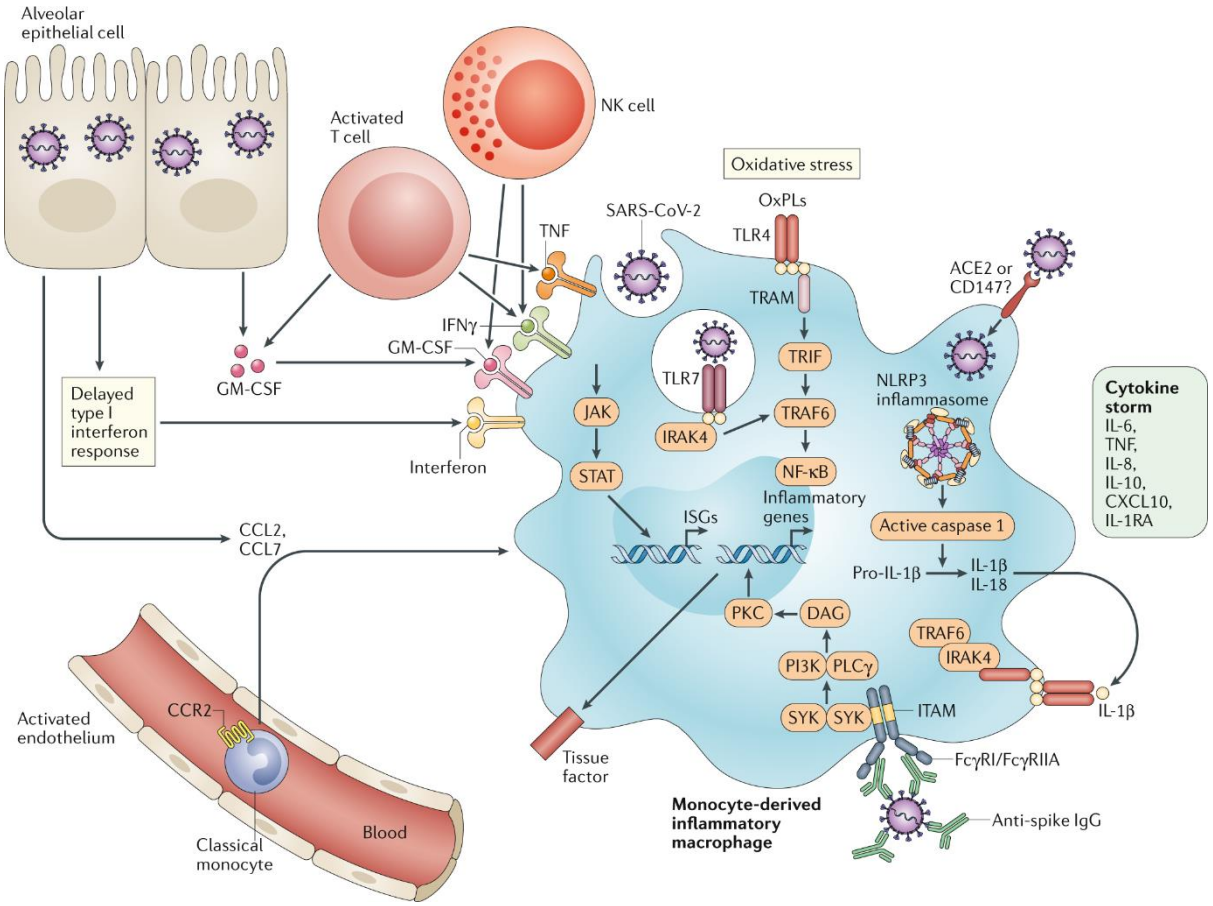

Figure. Mechanisms that likely contribute to the hyperactivation of monocyte-derived macrophages that is seen in patients with COVID-19. Activated monocyte-derived macrophages contribute to the COVID-19 cytokine storm by releasing massive amounts of pro-inflammatory cytokines. CCL, CC-chemokine ligand; CXCL10, CXC-chemokine ligand 10; ISG, interferon-stimulated gene; ITAM, immunoreceptor tyrosine-based activation motif; TRAM, TRIF-related adaptor molecule. Figure taken from Merad & Martin (2020), Nature Reviews Immunology.

Source: Merad & Martin (2020), Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nature Reviews Immunology.
https://www.nature.com/articles/s41577-020-0331-4

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3. Replacement of tissue resident alveolar macrophages with recruited inflammatory monocytes, neutrophils, and macrophages and an altered CD8+ T cell cytotoxic response, in severe cases compared to mild cases. Bost et al. using Viral-Track, a computational method that globally scans unmapped scRNA-seq data for the presence of viral RNA, enabling transcriptional cell sorting of infected versus bystander cells, to Bronchoalveloar-Lavage samples from severe and mild COVID-19 patients revealed a dramatic impact of the virus on the immune system of severe patients compared to mild cases. Their analysis shows a dramatic impact of the SARS-CoV-2 virus on the immune system of severe patients, including replacement of the tissue resident alveolar

macrophages with recruited inflammatory monocytes, neutrophils, and macrophages and an altered CD8+ T cell cytotoxic response, compared to mild cases. They find that the SARS-CoV-2 mainly infects the epithelial and macrophage subsets. In addition, Viral-Track detected an unexpected co-infection of the human Meta-pneumovirus in one of the severe patients, present mainly in monocytes perturbed in type-I IFN-signaling.

Source: Bost et al. (2020) Host-viral infection maps reveal signatures of severe COVID-19 patients. Cell. https://doi.org/10.1016/j.cell.2020.05.006

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4. Anti-inflammatory or cytokine storm inhibition – Tocilizumab, digitoxin, JAK1 inhibition, Atazanavir

Guo et al performed preliminary studies of single-cell transcriptomes of 13,289 peripheral blood mononuclear cells isolated at three longitudinal stages from two severe COVID-19 patients treated with **Tocilizumab**. They identified a severe stage-specific monocyte subpopulation and these cells centric immune cell interaction network connected by the inflammatory cytokines and their receptors. They demonstrated that Tocilizumab attenuated the over-activated inflammatory immune response. However, Immune cells including plasma B cells and CD8+ T cells still exhibited an intense humoral and cell-mediated anti-virus immune response in recovered COVID-19 patients.

Source: Chuang et al. *Preprint*. Tocilizumab treatment in severe COVID-19 patients attenuates the inflammatory storm incited by monocyte centric immune interactions revealed by single-cell analysis https://www.biorxiv.org/content/10.1101/2020.04.08.029769v1

Pollard et al suggest digitoxin to have therapeutic potential for both influenza and coronavirus. They demonstrated that cardiac glycoside **digitoxin** suppresses the hyper-proinflammatory response that is produced in host airway by influenza virus strain A/Wuhan/H3N2/359/95 in the cotton rat lung. Other reduced cytokines in this study were TNFα, GRO/KC, MIP2, MCP1, TGFβ, and IFNγ.

Source: Pollard et al. *Preprint*. Classical drug digitoxin inhibits influenza cytokine storm, with implications for COVID-19 therapy
https://www.biorxiv.org/content/10.1101/2020.04.09.034983v2

Tuttle et al showed in a murine model demonstrated that **inhibiting JAK1 kinase** can prevent pathology and mortality caused by a rampant innate immune response. They used a mouse model of Down syndrome (DS) with a segmental duplication of a genomic region encoding four of the six interferon receptor genes (Ifnrs) and showed these mice overexpress Ifnrs and are hypersensitive to IFN stimulation. Challenging these mice with viral mimetics activating toll-like receptor signalling and IFN ant-viral response, they demonstrated that the mice overproduced key cytokines, exacerbated liver pathology, rapidly lost weight, and died. This immune hypersensitivity and liver hyperinflammation were blocked by JAK1-specific inhibitor and suggest JAK1 inhibition could serve as a potential strategy to attenuate cytokine storm. This study also proves that people with down syndrome, carrying an extra copy of IFNR gene cluster encoded on chromosome 21 are considered high risk for Covid-19.

Source: Tuttle et al. *Preprint*. JAK1 inhibition blocks lethal sterile immune responses: implications for COVID-19 therapy.
https://www.biorxiv.org/content/10.1101/2020.04.07.024455v1

Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production. The identification of clinically approved drugs to be repurposed to combat 2019 CoV disease (COVID-19) would allow the rapid implementation of potentially life-saving procedures.The major protease (Mpro) of SARS-CoV-2 is considered a promising target, based on previous results from related CoVs with lopinavir (LPV), an HIV protease inhibitor. However, limited evidence exists for other clinically approved antiretroviral protease inhibitors.

Atazanavir (ATV) is of high interest because of its bioavailability within the respiratory tract. Results showed that ATV could dock in the active site of SARS-CoV-2 Mpro, with greater strength than LPV. ATV blocked Mpro activity. The study confirmed that ATV inhibits SARS-CoV-2 replication, alone or in combination with ritonavir (RTV) in Vero cells, human pulmonary epithelial cell line and primary monocytes, impairing virus-induced enhancement of IL-6 and TNF-α levels. These data strongly suggest that ATV and ATV/RTV should be considered among the candidate repurposed drugs undergoing clinical trials in the fight against COVID-19.

Source: Fintelman-Rodrigues et al. *Preprint*. Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production.
https://www.biorxiv.org/content/10.1101/2020.04.04.020925v2

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5. LY6E impairs coronavirus fusion and confers immune control of viral disease

Interferon-inducible lymphocyte antigen 6 complex, locus E (LY6E) potently restricts cellular infection by multiple CoVs, including SARS-CoV, SARS-CoV-2, and Middle East respiratory syndrome coronavirus (MERS-CoV). Mechanistic studies revealed that LY6E inhibits CoV entry into cells by interfering with spike protein-mediated membrane fusion. Importantly, mice lacking Ly6e in hematopoietic cells were highly susceptible to murine CoV infection.

Viral pathogenesis in Ly6e knockout mice was accompanied by loss of hepatic and splenic immune cells and reduction in global antiviral gene pathways. Ly6e directly protects primary B cells and dendritic cells from murine CoV infection.

Result: Y6E is a critical antiviral immune effector that controls CoV infection and pathogenesis.

Source: Stephanie Pfaender, Katrina B. Mar, Eleftherios Michailidis, Annika Kratzel, Dagny Hirt, Philip V'kovski, Wenchun Fan, Nadine Ebert, Hanspeter Stalder, Hannah Kleine-Weber, Markus Hoffmann, H. Heinrich Hoffmann, Mohsan Saeed, Ronald Dijkman, Eike Steinmann, Mary Wight-Carter, Natasha W. Hanners, Stefan Pöhlmann, Tom Gallagher, Daniel Todt, Gert Zimmer, Charles M. Rice, John W. Schoggins, Volker Thiel. *Preprint.* LY6E impairs coronavirus fusion and confers immune control of viral disease**.** bioRxiv 2020.03.05.979260; doi: https://doi.org/10.1101/2020.03.05.979260

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6. Monalizumab could restore the function of CD8+ T and NK cells, which were compromised by SARS-CoV2. They showed 80% of the patients were asymptomatic/mild symptoms and the rest exhibited severe symptoms. The severe group developed pneumonia and lymphopenia, with high levels of inflammatory cytokines in the plasma, indicating cytokine storm. Infected patients show overexpression of the inhibitor receptor NK group 2 member A (NKG2A) on CD8+ T cells and NK cells, which exhaust these types of cells and compromises innate immunity. Blocking this receptor restores cell function. A recent proposed mechanism for SARS-CoV2 is the induction of the expression of NKG2A and observed in the infected patients. Monalizumab is a NKG2A inhibitor. This drug was developed to limit the growth of some cancers which also show high expression of NKG2A and it is currently on phase 2 of clinical trial, showing promising results in cancer model without significant side effects. These researchers claim that patients with severe symptoms for SARS-CoV could perhaps benefit from being treated with Monalizumab, in combination with other drugs such as chloroquine and interferons.

Source: Ahmed Yaqinuddin & Junaid Kashir. Innate immunity in COVID-19 patients mediated by NKG2A receptors, and potential treatment using Monalizumab, Chloroquine, and antiviral agents. Medical hypothesis, April 2020
https://doi.org/10.1016/j.mehy.2020.109777

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