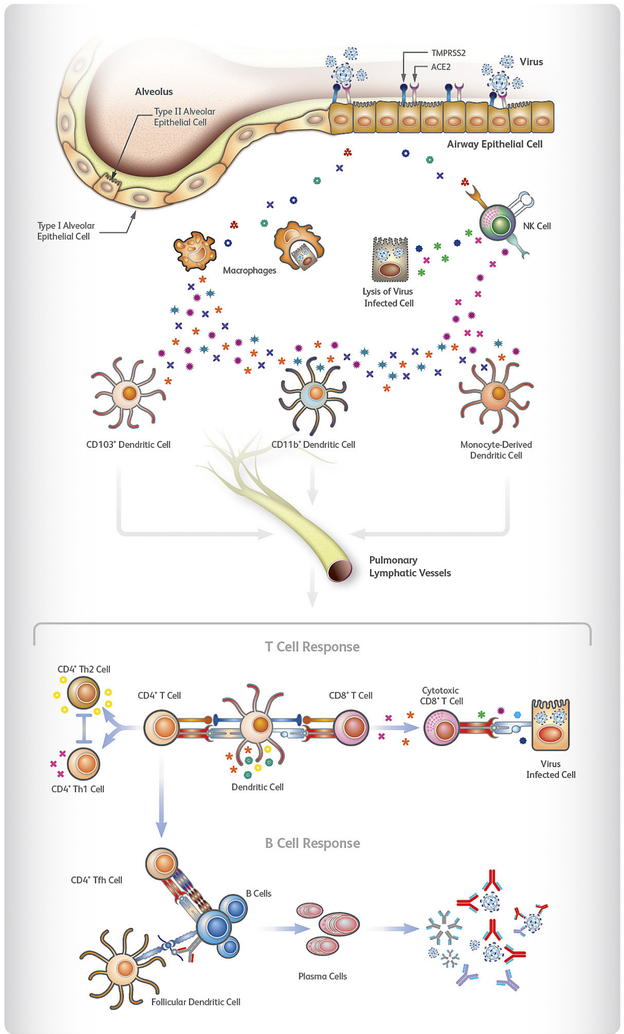
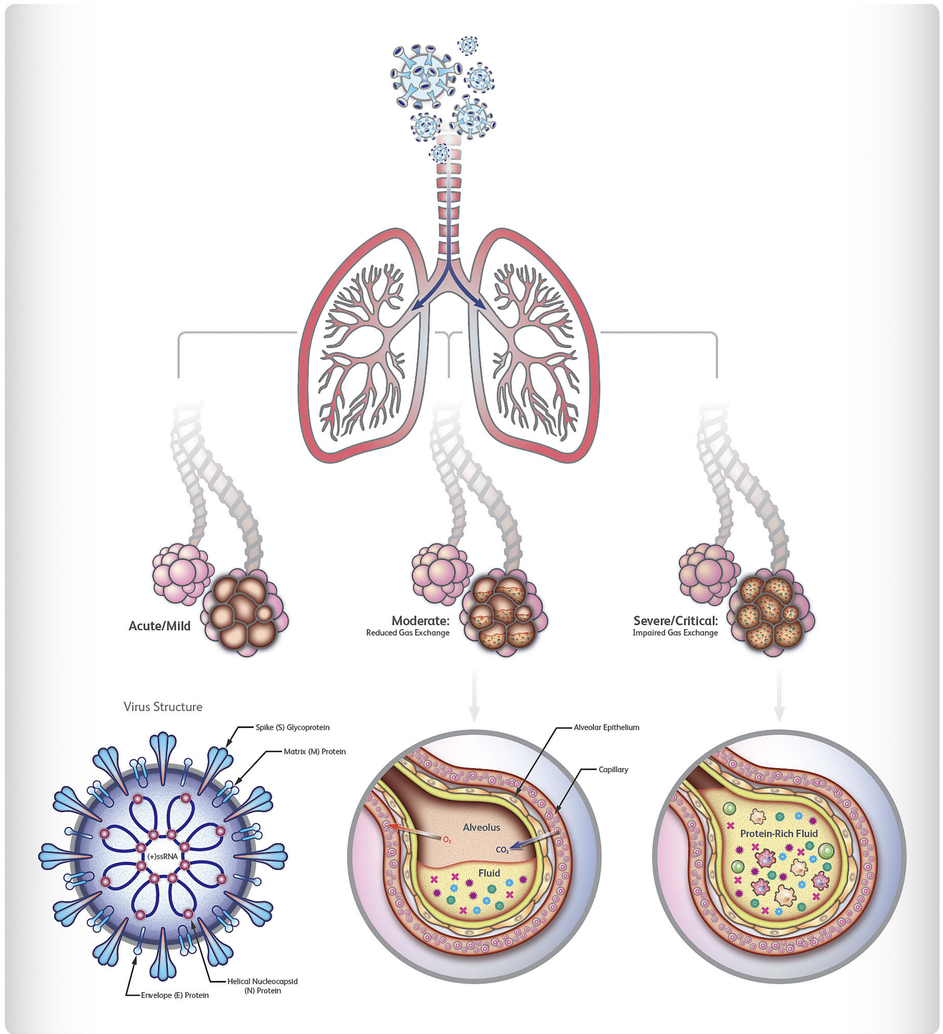
COVID-19: Snapshot of the Immune Response

Functional and Dysfunctional Immune Response to SARS-CoV-2

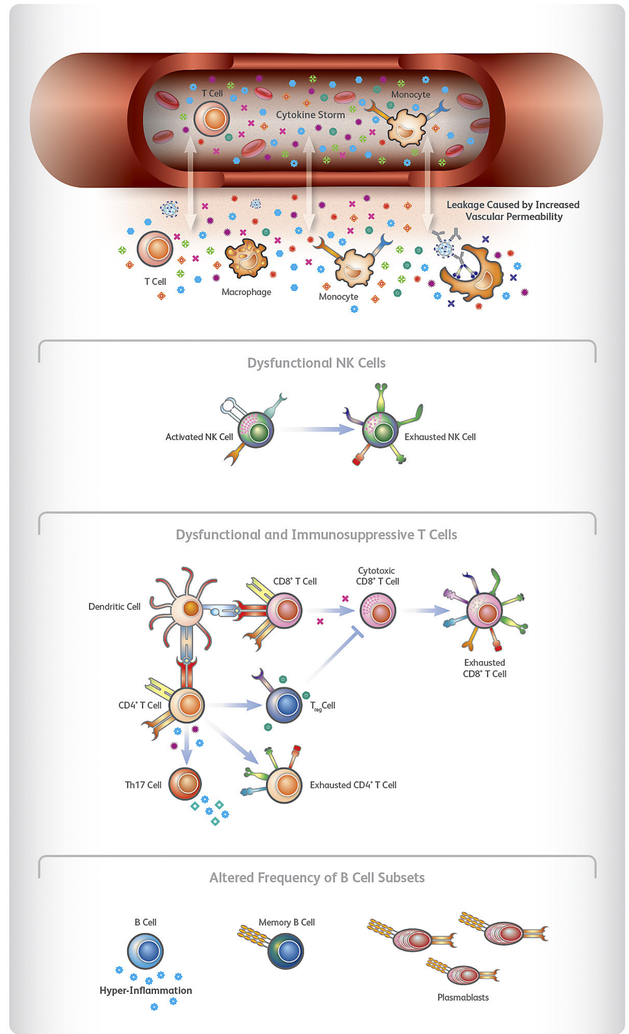
Functional Immune Response



Pathobiology of SARS-CoV-2



Dysfunctional Immune Response



Functional Immune Response

Upon infection, the virus attacks respiratory epithelial cells through the host receptors angiotensin-converting enzyme 2 (ACE2) and the transmembrane protease, serine 2 (TMPRSS2). Recognition of the invading virus leads to production of proinflammatory cytokines such as type I IFNs, CCL2, IL-18 and IL-1β. These mediators further promote macrophages, fibroblasts and other cells to produce more cytokines. Virus-infected cells undergo apoptosis and can be engulfed by macrophages.

Natural killer (NK) cells are another type of innate immune lymphocyte that represent the first line of defense against viral infections. Type I IFNs not only inhibit viral replication but also promote NK cell-mediated cytotoxicity. NK cells can directly kill infected cells through the release of granules containing cytotoxic mediators such as perforin and granzyme, during which process the expression of CD107a is upregulated. Additionally, the robust ability of NK cells to produce IFNγ boosts anti-viral immunity.

The enhanced cytokine and chemokine production facilitate the maturation of tissue-resident CD103$^+$ DC, activation of the CD11b$^+$ DC and recruitment of monocyte-derived DC from peripheral blood. After antigen acquisition, activated DC migrate out of the infected lung through pulmonary lymphatic vessels to the lymph nodes. Once in the lymph nodes, these DC initiate an adaptive immune response to fight against the virus.

T Cell Response

Following the uptake of viral antigens, CD86$^+$ activated DC produce cytokines to prime and present viral antigens to T cells. T cells recognize viral peptides presented by MHC molecules through the T cell receptors, resulting in T cell activation. In COVID-19 patients, considerable proportions of CD4 and CD8 T cells co-express HLA-DR and CD38, markers of activated T cells during infection. Depending on the cytokine signal, CD4 T cells can be differentiated into T helper 2 (Th2) or T helper 1 (Th1) cells. IFNγ produced by Th1 cells stimulates CD8 T cells to differentiate into cytotoxic T lymphocytes (CTL), inhibits Th2 cell differentiation and induces B cell differentiation to immunoglobulin production. By releasing cytolytic mediators such as perforins and granzymes, CTL inhibit virus replication through the lysis of virus-infected cells.

B Cell Response

Follicular dendritic cells retain large amounts of complement-tagged immunocomplexes and facilitate the capture of antigens by B cells. Activated CD4 T cells primed by viral antigens lead to the generation of CD4 T follicular helper cells (Tfh) that are essential for an effective humoral immune response. Upon interaction with cognate B cells, Tfh cells promote the proliferation and differentiation of B cells into antibody-secreting plasma cells. Virus-specific immunoglobulin (Ig) M, IgA and IgG produced by the plasma cells can neutralize virus infectivity. Alveolar macrophages recognize antibody-opsonized virus particles and clear them by phagocytosis.

Taken together, these effective immune responses result in containment of virus replication, minimal lung damage and possible recovery.

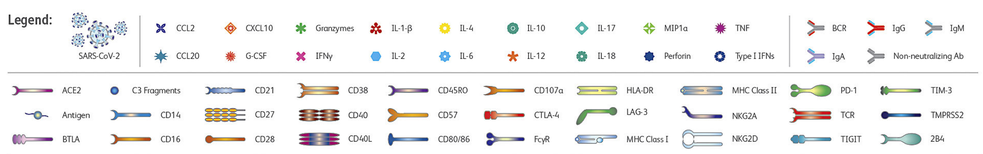
Pathobiology of SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel β-coronavirus and the causative agent of the coronavirus disease 2019 (COVID-19) pandemic. Millions of COVID-19 confirmed cases have been reported globally, therefore, understanding the pathogenesis and immunological processes in response to this infectious agent is crucial to develop therapeutic strategies to overcome the virus.

SARS-CoV-2 is an enveloped and single-stranded RNA virus with a membrane composed of several structural proteins including the matrix (M) protein, spike (S) glycoprotein and envelope (E) protein. Inside the membrane, the positive-sense RNA forms the viral genetic content by binding to helical nucleocapsid (N) proteins.

Once respiratory droplets containing the virus are inhaled, viruses can enter alveoli, where immune responses take place. During early and moderate infection, the anti-viral immune responses are predominately characterized by a strong wave of type I interferon (IFN) produced mainly by dendritic cells (DC) and epithelial cells followed by T cell-mediated cytotoxicity. In severe cases of infection, the immune cells such as monocytes, neutrophils and macrophages infiltrate into alveoli, producing a large amount of proinflammatory cytokines in a process characterized as cytokine storm. This burst of immune overreaction is associated with increased vascular permeability and accumulation of fluid in alveoli with severe cases progressing to acute respiratory distress syndrome.

Legend:



Abbreviations:

2B4, CD244; **Ab**, Antibody; **BTLA**, CD272, B- and T-lymphocyte attenuator; **CCL**, Chemokine (C-C motif) ligand; **CCL2**, Chemokine (C-C motif) ligand 2, monocyte chemoattractant protein 1 MCP1; **CCL20**, Chemokine (C-C motif) ligand 20, macrophage inflammatory protein-3 **MIP3A**; **CTLA-4**, CD152, cytotoxic T-lymphocyte-associated protein 4; **CXCL10**, C-X-C motif chemokine 10; **G-CSF**, Granulocyte-colony stimulating factor; **HLA-DR**, Human leukocyte antigen – DR isotype; **IFN**, Interferon; **IL**, Interleukin; **LAG-3**, CD223, lymphocyte-activation gene 3; **MHC**, Major histocompatibility complex; **MIP1α**, Macrophage inflammatory protein 1 alpha, chemokine (C-C) motif ligand 3 CCL3; **NKG2A**, CD159; **NKG2D**, CD314; **PD-1**, CD279, programmed cell death protein 1; **TIGIT**, T cell immunoreceptor with Ig and ITIM domains; **TIM-3**, CD366, T-cell immunoglobulin and mucin-domain containing-3; **TNF**, Tumor necrosis factor.

Dysfunctional Immune Response

The production of proinflammatory cytokines and chemokines trigger the recruitment of T cells, macrophages and monocytes to the site of infection. The increased vascular permeability leads to leakage of those cells into the circulation. The vast release of cytokines from those cells can result in cytokine storm, promoting widespread inflammation, lung infrastructure damage and even multi-organ failure. It has been observed that severe COVID-19 patients show higher plasma levels of IL-2, IL-10, TNFα, MIP1α and other inflammatory mediators. Peripheral IL-6 levels continue to increase during disease progression. Elevated frequency of CD14$^+$CD16$^+$ inflammatory monocytes in the peripheral blood has been observed and may contribute to the cytokine storm. Additionally, non-neutralizing antibodies bind with both viral particles and Fc receptors on macrophages or other cells to trigger proinflammatory cytokine production. This process, known as antibody-dependent enhancement, can promote inflammation and tissue injury.

NK cell-mediated killing depends on the integration of activating and inhibitory signals. NK cells can enter an exhausted state during chronic infection, displaying reduced expression of activating receptors such as NKG2D and 2B4 and increased expression of immune checkpoint receptors such as NKG2A.

Dysfunctional and Immunosuppressive T Cells

CD4 T cells can produce cytokines and prime both CD8 T cells and B cells. However, activated CD4 T cells can be differentiated into regulatory T cells (T_{reg}), a group of immunomodulatory cells that can limit the efficacy of antiviral protective immunity. It has been reported that the frequency of CD45RA$^+$ naive T_{reg} decreases during the progression of SARS-CoV-2 infection in blood, suggesting those naive T_{reg} might be converted to their memory counterpart CD45RO$^+$ T_{reg}. Another type of immune cell derived from CD4 T cells is the T helper 17 (Th17) cell. The production of IL-17 from Th17 cells can prevent differentiation of Th1 cells, inhibit secretion of the cytokines and recruit neutrophils, leading to viral persistence.

T cells play a key role in orchestrating virus-specific adaptive immune responses. However, both CTL and CD4 T cells can enter an exhaustion state that is characterized by an increased expression of immune inhibitory receptors such as PD-1, CTLA-4 and TIGIT and reduced T cell effector functions. Patients with COVID-19 have a higher amount of CD8 T cells expressing CD57, a key marker associated with replication senescence and reduced proliferation abilities. Severe COVID-19 patients exhibit lower expression of the co-stimulatory molecule CD28, which plays a central role in T cell activation. CTL can also become susceptible to apoptosis, possibly contributing to the reduced T cell count in blood.

Altered Frequency of B Cell Subsets

B cells are of key importance in the protective humoral immune response and possibly providing long-term protection against infection. The composition of B cell subpopulations changes in the blood of COVID-19 patients. The frequency of CD27$^+$ memory B cells decreases while the ratio of CD27$^+$CD38$^+$ plasmablasts increases in the B cell compartment in severe patients. Generation of plasmablasts is often correlated to immune protection against infection, however, it is possible that the plasmablast response is associated with inflammation. Indeed, B cells can produce IL-6, driving the germinal center formation and possibly exacerbating inflammation. Further studies on examining the antibody features produced from those plasmablasts are crucial to gain insights for vaccine development.

The information on COVID-19 presented in this poster is relevant as of June 2020. For a list of references, please contact your local sales representative.

For Research Use Only. Not for use in diagnostic or therapeutic procedures.

23-22829-00

BD Life Sciences, San Jose, CA, 95131, USA | Visit bdbiosciences.com