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A Canadian perspective on severe acute respiratory syndrome coronavirus 2 infection and treatment: how prevalent underlying inflammatory disease contributes to pathogenesis

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Running title: SARS-CoV-2 and COVID-19 in Canada

Abstract: The coronavirus disease 2019 (COVID-19), a serious respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global pandemic. Canada reported its first case of COVID-19 on 25th January 2020. By March 2020 the virus had spread within Canadian communities reaching the most frail and vulnerable elderly population in long-term care facilities. The majority of cases were reported in the provinces of Quebec, Ontario, Alberta and British Columbia and the highest mortality was seen among individuals aged 65 years or older. Canada has the highest prevalence and incidence rates of several chronic inflammatory diseases, such as multiple sclerosis, inflammatory bowel disease and Parkinson's disease. Many elderly Canadians also live with comorbid medical illnesses, such as hypertension, diabetes, cardiovascular disease and chronic lung disease and are more likely to suffer from severe COVID-19 with a poor prognosis. It is becoming increasingly evident that underlying inflammatory disease contributes to SARS-CoV-2 pathogenesis. Here, we review the mechanisms of SARS-CoV-2 infection and the host inflammatory responses that lead to resolution or progression to severe COVID-19 disease. Furthermore, we discuss the landscape of COVID-19 therapeutics that are currently in development in Canada.

Keywords: Canada, COVID-19, Coronavirus, Inflammation, Therapeutics, Chronic Disease

Introduction

In the past two decades, three novel human coronaviruses (HCoVs) have caused millions of infections worldwide and resulted in hundreds of thousands of deaths: severe acute respiratory syndrome coronavirus (SARS-CoV; 8089 confirmed cases, mortality rate ~9.6%, source: World health organization (WHO)), Middle East respiratory syndrome coronavirus (MERS-CoV; 2494 confirmed cases, mortality rate ~35%, source: WHO) and the most recent severe acute respiratory syndrome coronavirus 2. Most recently, SARS-CoV-2 has impacted our world – medically, socially and economically. As of September 8th, 2020, SARS-CoV-2 has spread to 188 countries, infected more than 27 million people worldwide and led to more than 890,000 deaths (John Hopkins University 2020b). SARS-CoV-2 was first identified in Wuhan, China in December of 2019 and by March 11th, 2020, the WHO declared COVID-19, the disease caused by SARS-CoV-2, a worldwide pandemic. Canada reported its first case of COVID-19 on January, 25th 2020 but by March 2020 the virus had spread throughout Canadian communities, reaching every province and all but one territory, with over 1000 confirmed and presumptive cases and 12 deaths (Government of Canada 2020a). As of September 8th, 2020, there are now over 132,000 confirmed cases in Canada and over 9146 deaths (Government of Canada 2020a). This rapid spread of COVID-19 in Canada has been approached with various public health interventions, including increased testing to identify infected individuals, increased contact tracing, and general public quarantine, all with various degrees of success. There is still much to learn about the biology of COVID-19, specifically how SARS-CoV-2 infects host cells and creates an uncontrolled inflammatory immune response in some patients while producing almost no symptoms in others. In this review, we will focus on the molecular mechanisms of SARS-CoV-2 infection and the inflammatory disease associated with COVID-19. We will begin with a brief exploration of the etiology of COVID-19 disease in Canada, including the risk factors

that may increase the susceptibility of Canadians to developing serious COVID-19 complications. Lastly, we will survey some of the made-in-Canada treatments and resources used to fight this mounting health pandemic that has put Canada and the rest of the world on pause.

The Canadian context and the burden of inflammatory disease

Like many western countries, Canada has one of the highest socio-demographic indexes in terms of life expectancy (82 yr) and health-adjusted life expectancy (71 yr) reflecting an aging population with increasing morbidity (Lang et al. 2018). Yet, while Canada has been relatively successful at controlling the spread of infection, Canada's death rate due to COVID-19 is relatively high compared to some other nations (e.g. Japan, Korea, New Zealand and Australia), with the majority of deaths occurring in long-term care homes (Government of Canada Public Health 2020; John Hopkins University 2020a). While more men than women are dying from COVID-19 worldwide, in Canada the reverse is true where ~55% of those that have died from COVID-19 have been women (Government of Canada Public Health 2020). There may be several factors that have contributed to this difference, and once the most active phase of this pandemic has passed, a comprehensive examination of its spread may reveal areas that were of particular concern in Canada relative to other countries. However, it is possible that at least two factors are contributing to the epidemiology of COVID-19 in Canada. First, Canada has a very large land mass, but a relatively small population and while Canada is the second largest country in the world, its 38 million inhabitants occupy 9,970,610 square km, a population density of about 4 persons per square km (Populationof.net 2020). Second, it is becoming clear that severe COVID-19 disease is associated with uncontrolled inflammation (Zhang et al. 2020a) and patients with chronic inflammatory disease such as obesity (Chiappetta et al. 2020) are more likely to have a poor disease outcome. Statistically, Canadians are more likely to suffer

from underlying inflammatory diseases – a situation that has sometimes been referred to as an "epidemic of inflammatory disease" (Stamper et al. 2016).

Persistent, low-grade inflammation is a risk factor for the development of many chronic diseases. In Canada, the incidence of chronic diseases has increased by ~14% every year over the past decade, imposing a major burden on the health care system (Elmslie 2016). Approximately 44% of adults over 20 years old in Canada have at least 1 of the 10 most common chronic conditions such as hypertension, osteoarthritis, osteoporosis, diabetes, asthma, chronic obstructive pulmonary disease, ischemic heart disease, cancer and dementia (Public Health Agency of Canada 2019). Three chronic inflammatory diseases are particularly prevalent in Canada and will be important for understanding how COVID-19 will impact the Canadian population: multiple sclerosis (MS), inflammatory bowel disease (IBD) and Parkinson's disease (PD). Canada has one of the highest rates of MS in the world, with almost 100 000 Canadians estimated to be living with the disease in 2018, 28% more than in Denmark, the country with the second highest rates of MS (Tracy 2015). Canada also has among the highest incidence and prevalence of IBD in the world (Kaplan et al. 2019) with approximately 270,000 Canadians living with the disease in 2018 and this number is predicted to rise to 403,000 Canadians by 2030. In 2017, 19.3% of Canadians aged 15 and older had arthritis, and women were 50-60 % more likely to suffer from this disease (Government of Canada Statistics Canada 2018; Ngo et al. 2014). Canada has the highest prevalence of PD in the world (G. B. D. Parkinson's Disease Collaborators 2018). Epidemiological, genetic and experimental evidence suggests that chronic neuroinflammation contributes to the progressive loss of neurons seen in chronic neurodegenerative diseases, including PD (Hirsch et al. 2012). Among the neurological disorders examined in the Global Burden of Disease, Injuries, and Risk Factors Study (GBD)

2015 (G. B. D. Neurological Disorders Collaborator Group 2015), PD was identified as the fastest growing neurological disorder in the world. Furthermore, genome-wide association studies (GWAS) and several epidemiological studies have identified a link between IBD and PD (Brudek 2019), suggesting that intestinal inflammation could be the silent driver of PD pathogenesis. Therefore, inflammatory disease is already a major concern in Canada and with the arrival of SARS-CoV-2, these pre-existing health conditions are likely to make the spread of this infection a unique challenge. Currently, many of the confirmed COVID-19 infections appear to be in Quebec and Ontario, but the majority of COVID-19-associated deaths (>80%) appear to be in long-term care homes in an aged population with several chronic conditions (Comas-Herrera A 2020) (Figure 1). Interestingly, while more men than women are dying from COVID-19 worldwide, in Canada the reverse is true where ~55% of COVID-19 deaths are women, mainly because vast majority of residents in the long-term care homes are older women (Government of Canada 2020b; Government of Canada Public Health 2020) (Figure 1). The Canadian population is unique in many ways from the rest of the world, and it is not surprising that COVID-19 would manifest itself differently in Canada compared to the rest of the world. Here, we will discuss the biology and pathogenesis of SARS-CoV-2 infection, with a focus on how the Canadian population could be affected.

The biology of coronaviruses

Coronaviruses (CoV) belong to the Coronaviridae family of viruses in the order Nidovirales and within the Coronavirinae subfamily there are four genera: the *alpha*, *beta*, *gamma* and *deltaCoV* (King et al. 2018). Recent epidemics or pandemics have been caused by three highly pathogenic *betaCoVs*: SARS-CoV, MERS-CoV and SARS-CoV-2, which replicate in the lower respiratory tract and can cause fatal pneumonia. In addition to these three highly pathogenic HCoVs, there are four less pathogenic HCoV strains, namely HCoV-OC43, HCoV-HKU1, HCoV-229E and HCoV-NL63, which replicate in the upper respiratory tract and cause only mild

symptoms (Gaunt et al. 2010; Shirato et al. 2014). With the exception of HCoV-229E and HCoV-NL63 (*AlphaCoV's*), HCoV's belong to the *betaCoV* genus.

Coronaviruses are spherical shaped enveloped viruses of approximately 60-125 nm in diameter. They contain the largest known non-segmented positive-sense single stranded RNA genome of approximately 27-32 kilobases (Gorbalenya et al. 2006) (Figure 2). Coronaviruses infect a wide range of species, including cattle, swine, birds, felines and humans (Cavanagh 2005; Fulton et al. 2011; Mora-Diaz et al. 2019; Pedersen et al. 2008; van der Hoek 2007; Vlasova et al. 2020) but have a propensity for zoonotic transmission, which makes them especially difficult to contain (Graham et al. 2013; Woo et al. 2009). Pathogenic HCoVs are associated with a wide range of respiratory illnesses, including common colds, pneumonia, and bronchiolitis (Matoba et al. 2015). Additionally, several studies have shown that HCoVs are also associated with a range of neurological (Arbour et al. 2000; Lau et al. 2004) and gastrointestinal symptoms (Wong et al. 2020) (Table 2).

SARS-CoV-2 entry and replication in target cells

The spike (S) protein is expressed on the surface of coronaviruses, giving the characteristic 'crown' appearance, and plays a critical role in determining tissue tropism (Hulswit et al. 2016). Similar to SARS-CoV, the S protein of SARS-CoV-2 binds with a strong affinity to human ACE2 (Yan et al. 2020). A recent study shows that neuropilin-1 (NRP1) could also act as a receptor for SARS-CoV-2 (Cantuti-Castelvetri et al. 2020). Table 1 summarizes a list of receptors on target host cells that binds to the S proteins of various *betaCoV* for initiation of cellular entry while Figure 3 represents a schematic diagram of coronavirus entry into target host cells.

It is entirely possible that SARS-CoV-2 utilizes other tissue-specific receptors for entry when the situation warrants – effectively choosing the appropriate route of entry based on the specific

membrane composition of the host cell. This is suggested by a recent study showing that SARS-CoV-2 infects and replicates within the human olfactory sensory neuron (Hoffmann et al. 2020b; Ou et al. 2020) even though WOM RNAseq analysis of macaque, marmoset and humans found that olfactory sensory neurons do not express the two key genes involved in SARS-CoV-2 entry, the ACE2 receptor and the serine protease TMPRSS2 (Bilinska et al. 2020; Brann et al. 2020). Therefore, it is more likely that synapse routes in the medullary cardiorespiratory center are facilitating entry through some other receptors such as mechanoreceptors or chemoreceptors (Natoli et al. 2020).

Clinical presentation of SARS-CoV-2 infection

COVID-19 has emerged as a complex multisystem clinical syndrome that is characterized as an illness with no symptoms, to mild, moderate or severe symptoms and the outcome of the disease is defined by the host immune responses. In a large cohort of 72,314 cases from the Chinese Centre of Disease Control and Prevention reported that 81% of patients had mild to moderate disease, 14% had severe pneumonia and 5% were critically ill (Wu and McGoogan 2020). Transmission from person to person occurs via respiratory droplets, aerosols, and via contaminated surfaces (Yao et al. 2020a). As with most coronaviruses, SARS-CoV-2 likely enters the host through mucosal barriers such as the nose, eyes and mouth. A recent study provided evidence for gastrointestinal infection of SARS-CoV-2, possibly by fecal-oral transmission route (Xiao et al. 2020). Virus can be detected before symptom onset and titers generally peak within a week after onset of symptoms (Pan et al. 2020). The symptoms of COVID-19 generally include fever, difficulty breathing and dry cough (Lai et al. 2020), but many individuals infected with SARS-CoV-2 remain asymptomatic (Day 2020). The exact proportion of asymptomatic individuals in the general population is currently a matter of debate and poses a problem for containing the spread of the disease. Viral loads are initially highest in the

nasopharynx but peak titers are usually reached several days later in the sputum (Huang et al. 2020b), suggesting that initial infection may begin in the nasopharynx and only later spread to the lungs. Many asymptomatic cases do show abnormalities in the lungs by CT scan, suggesting virus may invade the lungs even in mild cases (Hu et al. 2020). While virus can be detected in asymptomatic individuals, viral loads tend to be lower than in individuals who develop symptoms (Zhou et al. 2020c), while highest viral loads are found in severe cases (Yu et al. 2020). Based on a study from Wuhan, China of hospitalized COVID-19 patients, it was shown that 50% of infected patients developed symptoms after 7 days and by day 14, all patients developed symptoms, which formed the basis for the 14 day quarantine period used by most public health authorities to contain spread of infection (Wolfel et al. 2020).

Upon SARS-CoV-2 infection, the host cells mount an acute inflammatory response by inducing the production of a plethora of cytokines, chemokines and lipid mediators of the innate and adaptive immune system to eliminate the pathogen and protect the host. Emerging evidence suggests that failure to resolve the acute inflammatory response leads to hyperinflammation and dysregulated adaptive immune response resulting in tissue injury and multi-organ failure, especially in the renal, cardiac and hepatic systems (Huang et al. 2020a; Xu et al. 2020c). In a retrospective study involving 52 critically ill patients admitted to intensive care unit with pneumonia, over 80% of the fatal cases were diagnosed with acute respiratory disease syndrome (ARDS) and multi-organ failure (Yang et al. 2020). It is becoming increasingly clear that SARS-CoV-2 initiates an uncontrolled systemic inflammatory disease in some patients.

SARS-CoV-2 infection activates the innate immune response and inflammation

Initial infection of SARS-CoV-2 in the respiratory tract likely results in the activation of the innate immune system. Upon induction of the innate immune responses, release of interferons (IFNs) by host cells serves as the first-line of defense against viral infection. In the early stages of viral

infection, type I and type III interferons (IFN-I and IFN-III) act as key regulators of antiviral immune responses that trigger the upregulation of IFN-stimulated genes (ISGs). ISGs have the ability to interfere with every step of the viral replication cycle and balance both pro-inflammatory and anti-inflammatory responses towards successful resolution of infection (Lazear et al. 2019). During infection with highly pathogenic coronaviruses, such as SARS-CoV, a delayed IFN-I response is associated with severe lung pathology. Both mice treated early with IFN-β and IFN receptor knockout mice showed better survival when infected with SARS-CoV than untreated, wild-type mice (Channappanavar et al. 2016). In a MERS-CoV mouse model, early treatment with interferon was also found to be protective, while delayed treatment only exacerbated inflammation (Channappanavar et al. 2019). Indeed, SARS-CoV encodes many proteins which interfere with the interferon pathway (McBride and Fielding 2012), and many of these ORFs are conserved in SARS-CoV-2 (Lu et al. 2020). Although all three viruses likely initially inhibit interferon expression from epithelial cells in the respiratory tract, SARS-CoV and MERS-CoV have been shown to induce release of interferon and several pro-inflammatory cytokines from monocyte derived macrophages and dendritic cells (Channappanavar and Perlman 2017). SARS-CoV-2 spike protein is also able to elicit expression of the pro-inflammatory cytokine IL-6 in the monocyte cell line THP-1 (Chen et al. 2020c). This response could lead to the release of chemokines that would recruit pro-inflammatory cells to the site of injury. Furthermore, ACE2 is upregulated by interferon, which could further promote viral spread and tissue injury (Ziegler et al. 2020). Hence, it is possible that a lack of interferon response early in infection allows a build-up of virus by replication in epithelial cells. These large titers of virus would then induce a large interferon response in immune cells that could cause runaway inflammation and tissue damage. This is further amplified in aged individuals as they might have an impaired capacity to mount type I and type III IFN responses (Molony et al. 2017). For SARS-CoV-2 infection, however, higher levels of serum IFN-α and greater expression of ISGs were found in mild cases as compared to severe and critical cases (Hadjadj et al. 2020),

suggesting interferon is protective at late stages of COVID-19. These differences may be due to the greater sensitivity of SARS-CoV-2 to type I IFNs, which is thought to be due to loss or disruption of key genes involved in IFN antagonism (Lokugamage et al. 2020) (Figure 2).

Once the initial phase of the innate immune response has been activated, a localized inflammatory response is initiated which involves orchestrated recruitment of specific subset of leukocytes that release chemokines needed to traffic effector cells to the site of infection. Although the factors separating mild COVID-19 cases from severe cases aren't entirely understood, the forces driving severe pathogenesis are thought to be similar to SARS-CoV and MERS-CoV (Figure 4). In infections by these viruses, overproduction of pro-inflammatory cytokines and chemokines, or hypercytokinemia, is thought to play a major role in pulmonary damage (Channappanavar and Perlman 2017) and patients with SARS-CoV-2, SARS-CoV and MERS-CoV show increased serum levels of multiple cytokines (Liu et al. 2020a; Zhang et al. 2004). The submucosal layer of the lungs are filled with immune cells that can release a large number of pro-inflammatory cytokines during infection, thereby recruiting macrophages, neutrophils and T cells. Mast cells, whose role in viral infections is often poorly understood, could also play a role in inflammation, releasing many of the cytokines implicated in SARS-CoV-2 pathogenesis and influencing macrophage activation (Kritas et al. 2020). It is increasingly evident that a dysfunctional host immune response and the failure of antiviral immunity to control SARS-CoV-2 drives the development of COVID-19. In a recent study, transcriptional profiling of various cells and serum from COVID-19 patients revealed that SARS-CoV-2 infection evokes a low antiviral type 1 IFN response, while inducing a consistent chemokine and pro-inflammatory cytokine signature consisting of IL-6, IL-1RA, CCL2, CCL8, CXCL2, CXCL8, CXCL9 and CXCL16, which act as chemoattractants for T cells, NK cells, neutrophils and monocytes/macrophages, respectively (Blanco-Melo et al. 2020). Also, abnormally high serum levels of C-reactive protein, ferritin, fibrinogen and D-dimer (degradation product of crosslinked

fibrin) has been reported in patients with severe COVID-19 (Liu et al. 2020b). There is some evidence that this uncontrolled inflammation could be affected by the age of the host. Older individuals have an altered immune response, sometimes referred to as hypercytokinemia, that may lack some of the feedback mechanisms that control the scope of the inflammatory response (Tisoncik et al. 2012), a situation very much mirroring the one observed in COVID-19 disease in the elderly. Hypercytokinemia is a common complication in the elderly sometimes caused by renal dysfunction, and systemic inflammatory response syndrome (SIRS) is an early sign of post-operative complications in elderly patients that have undergone gastrointestinal surgery (Beppu et al. 2003; Ono et al. 2001). Therefore, older adults would be more likely to suffer from hypercytokinemia in response to SARS-CoV-2 infection. In support of this notion, older macaques infected with SARS-CoV developed more severe pathology than younger adult macaques and, though they have similar viral titers, produce higher levels of pro-inflammatory cytokines (Smits et al. 2010).

The serum levels of several cytokines are dramatically increased in severe COVID-19 disease as compared with patients that have milder disease. For example, IL-6 is thought to be one of the key cytokines involved in SARS-CoV-2 pathogenesis, as high serum levels have been associated with more severe disease (Akbari et al. 2020; Kermali et al. 2020). IL-6 is a pro-inflammatory cytokine involved in activation of the acute phase response and controlling the activity of various immune cells (Tanaka et al. 2014). Notably, IL-6 is both secreted by macrophages and induces monocyte differentiation into macrophages (Akira and Kishimoto 1996), which could lead to a positive feedback loop, possibly contributing to hypercytokinemia. IL-6 also induces the differentiation of naive T-cells to T_H17 cells, which release the pro-inflammatory cytokine IL-17 (Kimura and Kishimoto 2010). While IL-17 is important in protection against bacteria and fungi, it is also known to be involved in many autoimmune diseases (Kimura and Kishimoto 2010) and data from *in vivo* acute lung injury models and MERS patients

suggest IL-17 may play an important part in these diseases (Pacha et al. 2020). Importantly, IL-17 has been implicated in the pathogenesis of SARS-CoV-2, as high levels of IL-17 were shown to be highly positively correlated with disease severity (Pacha et al. 2020).

Although it is well established that T-cells produce IL-17, increasing evidence demonstrates that innate immune cells, such as neutrophils and mast cells can also produce IL-17 (Xu and Cao 2010). The production of IL-17 by these cells orchestrates innate immune responses against extracellular pathogens by inducing the formation of extracellular traps, known as neutrophil extracellular traps (NETs) and mast cell extracellular traps (MCETs), respectively (Lin et al. 2011; von Kockritz-Blickwede et al. 2008). NETs are extracellular web-like structures that consists of a backbone of chromatin (DNA and histones), antimicrobial proteins and proteases that are released from the neutrophils that entrap and kill pathogens to limit infections. A recent study showed that increased numbers of neutrophils and higher levels of NET biomarkers, namely myeloperoxidase-DNA (MPO-DNA) complexes and citrullinated histone H3 (Cit-H3) have been detected in the sera of COVID-19 patients (Zuo et al. 2020). NETs might be the drivers of the microvascular thrombosis that is increasingly seen in COVID-19 patients, possibly due to the toxic NET cargo that could promote blood coagulation and blockage of small blood vessels as seen in acute lung injury and acute respiratory disease syndrome (ARDS), leading to death. The involvement of MCETs in COVID-19 has not been examined in the literature yet.

Another pro-inflammatory cytokine, IL-1β, is also elevated in the plasma of SARS-CoV-2 infected patients, but is not associated with severe disease (Akbari et al. 2020; Huang et al. 2020a). Mature IL-1β is released from cells following processing of the pro-IL-1β by the NLRP3 inflammasome, a multi-protein complex that is activated by molecular patterns associated with

infection, such as viral RNA, and cellular damage, such as ATP (Franchi et al. 2012). Notably, serum lactate dehydrogenase (LDH) levels are commonly high in SARS-CoV-2 patients with severe disease (Kermali et al. 2020), which indicates induction of a highly inflammatory form of programmed cell death, called pyroptosis, mediated by the NLRP3 inflammasome (Jia et al. 2019). It has previously been suggested that activation of the NLRP3 inflammasome and pyroptosis may play a substantial role in COVID-19 disease progression (Yap et al. 2020). Notably, SARS-CoV E and ORF3a, which share significant homology with SARS-CoV-2 E and ORF3a, respectively (Figure 2), are known to activate the NLRP3 inflammasome (Chen et al. 2019; Nieto-Torres et al. 2015; Siu et al. 2019). This indicates that direct activation of pro-inflammatory pathways, like the NLRP3 inflammasome, by SARS-CoV and SARS-CoV-2 could be important for viral replication and pathogenesis.

IL-10 is another cytokine that is commonly found at higher levels in the plasma of SARS-CoV-2 patients, especially those with severe disease requiring hospitalization (Akbari et al. 2020). IL-10 is an anti-inflammatory cytokine and is often exploited by viruses to establish persistent infections (Rojas et al. 2017). Though it is possible that IL-10 could inhibit T-cell responses towards the virus (Rojas et al. 2017), it is difficult to discern whether IL-10 is a cause or consequence of SARS-CoV-2 pathogenesis. In a MERS-CoV mouse model, the differences in IL-10 induction by virus infected young and aged mice is most stark of any cytokines tested (Yao et al. 2020b), which could have implications for understanding why elderly populations experience higher mortality rates than younger populations.

SARS-CoV-2 and adaptive immune responses

During the late stage of viral infection, the adaptive immune responses act as the second line of defense and generate specific neutralizing antibodies that are required for the elimination and clearance of the virus-infected cells. MERS-CoV, but not SARS-CoV, has been shown to

directly infect primary PBMC-derived T-cells and induce their apoptosis (Chu et al. 2016), further inhibiting a major mechanism for viral clearance and immunomodulation. A marker of apoptosis, Annexin-V, was increased on T-cells isolated from the blood of patients with severe COVID-19, suggesting that SARS-CoV-2 may be able to induce apoptosis, though whether this is through direct infection of the T cell or another mechanism like bystander effect is not currently known (Hadjadj et al. 2020). Post-mortem examinations revealed that SARS-CoV-2 invaded the lymph nodes and spleens, causing structural damage and lymphocyte apoptosis (Chen et al. 2020c). Notably, lymphopenia, or low levels of lymphocytes like T and B cells, is common in all three severe coronavirus diseases (Assiri et al. 2013; Hui et al. 2003; Li et al. 2020a), and was more common in severe cases of COVID-19 (Akbari et al. 2020; Kermali et al. 2020). The proportion of naive T-helper cells in peripheral blood was also increased in severe cases (Qin et al. 2020).

In a retrospective, single-center study with a cohort of 452 COVID-19 patients from Wuhan, China reported a dysregulated immune system, specifically with a low $CD4^+$ T-lymphocyte count (Qin et al. 2020). Since then many more studies have been conducted and similarly report a dramatic reduction in the total number of T lymphocytes, particularly $CD4^+$ and $CD8^+$ T-cells in severe COVID-19 patients which also correlates with disease severity (Diao et al. 2020). Notably, surviving $CD4^+$ and $CD8^+$ T-cells expressed PD-1 and Tim-3, markers of T-cell exhaustion. In this study, PD-1 and Tim-3 expression on T-cells was monitored by flow cytometry during disease progression in three patients. Interestingly, PD-1 and Tim-3 were expressed at low levels in $CD4^+$ and $CD8^+$ T-cells in the prodromal COVID-19 disease, however, surface expression of these markers on $CD8^+$ T-cells progressively increased during symptomatic and ICU disease stages (Diao et al. 2020). Although these findings need to be

replicated in a large cohort of COVID-19 patients, it suggests that disease severity may be a driver of T-cell depletion/exhaustion. More recently, a deep characterization of bulk T-cells from 39 COVID-19 patients also revealed that $CD4^+$ and $CD8^+$ T-cells display markers of exhaustion/senescence ($PD1^+CD57^+$) (De Biasi et al. 2020). Although $CD57^+$ T-cells from COVID-19 patients showed decreased proliferation *in vitro* after antigen-specific stimulation, it is not clear whether the COVID-19 patients' T-cells are functionally exhausted. CD57 is considered a surrogate marker of senescence which has been associated with aging, chronic infections and inflammatory diseases (Pinti et al. 2016). Similar to T-lymphocytes, NK cell counts were also markedly decreased and express markers of exhaustion in COVID-19 patients compared with healthy subjects (Zheng et al. 2020). The expression levels of the inhibitory receptor, NKG2A was increased which has been shown to induce NK cell exhaustion in chronic viral infections (Zhang et al. 2019). Furthermore, $NKG2A^+$ cells also had a reduced ability to produce IFN-γ, IL-2, granzyme B and TNF-α. Taken together, these findings support the notion that functional exhaustion of T cells and NK cells by SARS-CoV-2 could lead to the breakdown of antiviral immunity at an early stage, resulting in viral persistence and disease progression.

Consequences of ARDS and cytokine storm syndrome (hypercytokinemia)

The immunopathogenesis of SARS-CoV-2 infection mirrors that of SARS-CoV and MERS-CoV, with an overt unregulated inflammatory response that results in pneumonia and ARDS. As discussed above, infection is initiated by binding of SARS-CoV-2 to the ACE2 receptor expressing cells in the airway that is more abundantly expressed by type II pneumocytes and to a lower extent by type I pneumocytes, alveolar epithelial cells and pulmonary endothelial cells (Hamming et al. 2004). Following replication and release of the virions, host cells undergo an inflammatory form of cell death known as pyroptosis and release damage-associated molecular patterns (DAMPs) which are recognized by neighbouring cells resulting in a wave of pro-

inflammatory cytokines and chemokines, including IL-6, IL-1RA, CCL2, CCL8, CXCL2, CXCL8, CXCL9 and CXCL16. The high levels of pro-inflammatory cytokines lead to massive recruitment of immune cell infiltrates (neutrophils, monocytes, dendritic cells, NK cells and T-cells) in the alveoli leading to a vicious cycle of amplification of inflammatory responses and lung damage with the formation of hyaline membranes and thickening of alveolar wall (Figure 5). Accumulating evidence suggests that the high levels of pro-inflammatory cytokines could lead to disruption of vascular endothelial barrier, loss of barrier integrity and activation of coagulation pathways (as indicated by elevated D-dimer levels), which is increasingly seen in severe COVID-19 patients (Becker 2020). It has been established that the aging immune system is associated with a decline in IFN-I responses (Shodell and Siegal 2002), which further decreases with viral infection (Canaday et al. 2010). It is plausible that this age- or viral-related IFN-I impairment may be associated with the release of uncontrolled pro-inflammatory cytokines and chemokines leading to pulmonary and intravascular complications seen in COVID-19 patients (McGonagle et al. 2020). Histopathological examination of lung tissue obtained by transthoracic biopsy from a 72 year old man with COVID-19 who had a history of hypertension and diabetes showed diffuse alveolar damage with type II pneumocyte hyperplasia, intra-alveolar fibrin, interstitial loose fibrosis and the presence of chronic inflammatory infiltrates (Zhang et al. 2020b). The CT scans of the chest also revealed multifocal nodular ground glass-like opacities. Despite antiviral treatments, the patient succumbed to COVID-19-induced injuries.

Effects on the Central Nervous System (CNS): An interplay between the lung and the brain may also explain how SARS-CoV-2 infection can rapidly progress to a more severe form of the disease. Experimentally induced lung injury causes neurological damage in pigs (Heuer et al. 2011). Furthermore, brain damage (acute intracranial hypertension) was found to induce symptoms of lung injury, and a combination of lung and brain injury appeared to have an additive effect on further damage to the lung/brain and release of pro-inflammatory cytokines

(Heuer et al. 2011). In fact, lungs from organ donors who die of traumatic brain injury (TBI) are often ineligible for transplant due to subsequent lung injury caused by neuronal cell death (Nicolls and Laubach 2014). This interaction between lung and brain suggests that SARS-CoV-2 may begin a cycle of injury between these two organs that could explain the rapid deterioration observed in severe cases. The importance of the lung-brain axis is underscored by high proportions of COVID-19 patients who exhibit neurological symptoms (Carod-Artal 2020; Li et al. 2020c). A particular area of concern underlies the possibility that SARS-CoV-2 could invade the -CNS (Alam et al. 2020), further exacerbating damage associated with the lung-brain axis (Li et al. 2020b). Finally, many of the studies which examined the lung-brain interactions have been done in the context of mechanical ventilation, with results suggesting that mechanical ventilation could be a possible driver of lung and neurological injury in patients with SARS-CoV-2 induced respiratory distress, which, in turn, could result in worse outcomes (Bilotta et al. 2019; Pelosi and Rocco 2011).

***Effects on the cardiovascular system*:** The effects of SARS-CoV-2 infection on the cardiovascular system are thought to play a major role in severe disease and mortality. The first line of evidence came from the findings that hypertension, cerebrovascular disease, and cardiac disease are three of the most prominent comorbidities associated with severe CoVID-19 (Wang et al. 2020a; Yang et al. 2020). Excessive thrombosis, or blood clot formation, and abnormal coagulation are common in COVID-19 patients in the ICU (Becker 2020). The effects of infection on platelets may play a role, as reduction in platelet counts in the blood, or thrombocytopenia, has been found in many COVID-19 patients and lower platelet levels is correlated with more severe disease and death (Xu et al. 2020a). High levels of D-dimer, an indicator of blood clot formation and/or breakdown, is also associated with higher mortality (Zhang et al. 2020c). How SARS-CoV-2 infection induces these effects is not known, but many mechanisms have been suggested. These include disrupting platelet production, platelet

destruction, or increasing platelet consumption in the lungs (Xu et al. 2020a). Hypercytokinemia is likely to play a role, with cytokines and inflammation possibly causing thrombosis in the lungs (McGonagle et al. ; Xu et al. 2020a). Release of extracellular nets, discussed above, is another major mechanism by which SARS-CoV-2 may cause thrombosis (Nicolai et al. 2020).

Infection of blood vessels by SARS-CoV-2 may play an important role in disease severity. ACE2 is expressed on endothelial cells (Hamming et al. 2004) and SARS-CoV-2 has been found to infect blood vessel organoids *in vitro* (Monteil et al. 2020). Lungs from patients who died from COVID-19 were found to have much more severe endothelial damage and thrombosis than lungs from patients who died from influenza (Ackermann et al. 2020). Viral proteins were found intracellularly in inflamed endothelium in lung, kidney and small bowel (Ackermann et al. 2020; Varga et al. 2020). Infection by SARS-CoV-2 or deposition of complement on the endothelium could not only disrupt its structure, but could lead to platelet activation and thrombosis (Pons et al. 2020). The SARS-CoV-2 receptor, ACE2, was also found to be expressed on pericytes in adult human heart, leading to speculation that they could be infected by SARS-CoV-2 (Chen et al. 2020b). Another study found SARS-CoV-2 viral RNA in the myocardium of patients who had died of COVID-19, with interstitial cells showing viral RNA by *in situ* hybridization (Lindner et al. 2020). Interactions between these cells and endothelial cells could be another route by which SARS-CoV-2 could cause damage to the endothelium. Widespread damage to the endothelium and blood clot formation would be expected to not only exacerbate lung damage but could lead to multiple organ failure. Ultimately, endothelial damage, lung damage and hypercytokinemia may act in concert to cause severe disease and death in SARS-CoV-2 infected patients.

COVID-19 disease progression: The progression of the disease in both mild and severe cases of SARS-CoV-2 infection is not clear, and will likely require substantial work in animal models to fully elucidate. Further complicating matters, the progression of disease is often highly variable

between individuals, even those with similar risk factors. Based on the evidence described above, it is possible that virus infection and pathogenesis generally unfold as follows. First, the virus initially infects cells of the nasopharynx and spreads to the lungs while inhibition of interferon allows the virus to build up to high levels, at least in cases that become symptomatic. The immune response is then initiated, either through substantial buildup of pathogen-associated molecular patterns (PAMPs), such as viral RNA/DAMPs or direct activation of innate immune cells. In mild cases, a robust interferon response and low amounts of inflammation would inhibit viral replication and spread. In severe cases, higher titers of virus would induce runaway inflammation through release of pro-inflammatory cytokines and further recruitment of leukocytes, while inhibition of T-cells would prevent efficient viral clearance. High levels of viral infection and inflammation could then lead to heavy lung dysfunction, setting up another destructive positive-feedback loop via the lung-brain axis and systematic damage through hypoxia. Further damage to the vasculature of the lungs by disruption of the endothelium and abnormal clotting would further exacerbate lung damage and could lead to multi-organ failure. Ultimately, the severity of the disease may be determined by the patient's ability to control viral replication while also limiting inflammation-related damage, which proves more difficult as viral titers increase. Pre-existing conditions that accelerate damage to the respiratory, circulatory or nervous system, inhibit viral clearance or enhance inflammation at later time points could also make patients more vulnerable to severe disease and death.

Interplay between SARS-CoV-2 and prevalent inflammatory diseases in Canada

Data of infection rate and mortality with respect to underlying health conditions is still unavailable, but some recently published case reports indicate that chronic inflammatory diseases exacerbate COVID-19 and may lead to poor outcomes. For example, multiple sclerosis may increase the incidence of infections in general and increase the risk of hospitalization from infectious diseases (Willis and Robertson 2020). Of a small cohort of MS

patients that were infected with SARS-CoV-2, most developed only mild infection (Bowen et al. 2020). Worryingly, two of the eight patients died and it was noted that these patients also had the most severe MS, suggesting those with worse MS are especially vulnerable to poor outcomes as a result of COVID-19 (Bowen et al. 2020). Although some treatments for MS may increase risk of infectious diseases (Willis and Robertson 2020), the possibility has also been raised that many of the drugs used to treat MS may improve outcomes after SARS-CoV-2 infection due to their immunomodulating abilities, including IFN-β, Ocrelizumab, and adamantanes (Hung et al. 2020; Novi et al. 2020; Rejdak and Grieb 2020; Valencia-Sanchez and Wingerchuk 2020). This does leave open the possibility that if some of these drugs are repurposed to fight COVID-19, MS patients could face shortages. Like MS, IBD patients could theoretically be at a higher risk of SARS-CoV-2 infection and mortality, and immunosuppressive therapies used could potentially enhance or suppress disease progression (Neurath 2020). Drugs that could exacerbate lymphopenia, like thiopurine and tofacitinib, and corticosteroids, whose use to treat CoVID-19 has been controversial, may exacerbate disease and should be used with caution (Neurath 2020). Other drugs that block inflammatory mediators, like anti-TNF-α, vedolizumab, ustekinumab, may instead prevent severe inflammation associated with COVID-19 (Neurath 2020). A study from Italy found no incidences of SARS-CoV-2 infection in a cohort of IBD patients while another found that, of those patients infected with SARS-CoV-2, mortality was not significantly higher than the general population (Norsa et al. 2020; Taxonera et al. 2020b). Unlike the general population, IBD patients did seem to exhibit high rates of gastrointestinal symptoms (Taxonera et al. 2020b).

Susceptibility of PD patients to severe COVID-19: There are no studies available yet showing that PD patients have an increased risk of COVID-19. It has previously been pointed out how the SARS-CoV-2 pandemic may negatively affect those with PD, although evidence suggests PD patients may not be at a higher risk of mortality (Helmich and Bloem 2020; Papa et al.

2020). It is still too early to predict if COVID-19 will have long-term neurological sequelae in PD patients because disease symptoms may develop over years and vary depending on the gender and age (at the time of infection) of patients. A recent study reported that PD patients with COVID-19 appears to have worsened motor as well as non-motor symptoms as compared to control patients (Cilia et al. 2020). In addition, PD patients infected with the virus experienced more daily “off” episodes – time period when symptoms are not adequately controlled (Cilia et al. 2020). SARS-CoV-2 is a novel virus and further research is needed to better elucidate the cause-and-effect relationship between clinical manifestations and disease pathogenesis.

Susceptibility of IBD patients to COVID-19 and predisposition of PD: Inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn’s disease, chronic immune-mediated inflammatory diseases of the gastrointestinal (GI) tract. Increasing evidence suggests that GI symptoms, such as diarrhoea, nausea and vomiting are frequent hallmarks of SARS-CoV-2 infection, especially in severe COVID-19 disease. Indeed, 10-12% of patients with COVID-19 manifest GI symptoms and viral RNA could be detected in the faeces of ~40% of the patients (Parasa et al. 2020). Interestingly, infectious SARS-CoV-2 has been isolated from these patients even after virus particles were not detectable in the sputum, supporting the notion that fecal-oral transmission may occur even after viral clearance. Immunohistochemical examination of GI tissues revealed that the ACE2 protein is abundantly expressed in the enterocytes of the GI tract and is further induced in the inflamed glandular epithelial cells of IBD patients, facilitating SARS-CoV-2 entry (Taxonera et al. 2020a; Xiao et al. 2020). In addition, numerous infiltrating plasma cells and lymphocytes with interstitial edema was seen in the lamina propria of the GI tract, supporting the involvement of the innate and adaptive immune system (Xiao et al. 2020). Although IBD patients could be at an increased risk of infection and mortality, at this time there is not enough evidence to support or refute this hypothesis and further studies are warranted (Neurath 2020).

Mounting evidence points to the role of the “gut-brain axis” in the development of PD, with chronic systemic inflammation, immune cell activation, gut microbiome dysbiosis and increased intestinal barrier permeability observed decades before the development of any motor symptoms (Brudek 2019). Ample amount of literature supports that chronic intestinal inflammation could be the silent driver of PD pathogenesis (Houser and Tansey 2017). The earlier work by Braak *et. al.* (2003),suggested that infection of the GI tract by a neurotropic viral pathogen probably results in the misfolding and aggregation of alpha-synuclein, which spreads from the enteric nervous system *via* the vagus nerve to the central nervous system. As the disease progresses aggregated alpha-synuclein spreads throughout the brain in a ‘prion-like’ manner infecting not only the dopaminergic neurons but also various other neuronal populations and consequently resulting in neurodegeneration. As chronic neurodegenerative diseases occur over years or decades, it is plausible that IBD patients infected with SARS-CoV-2 may have an accelerated disease progression and there might be an upsurge in the burden of PD. Therefore, IBD patients who have recovered from COVID-19 disease should be closely monitored over long time period. In line with this, there is an international database that is established by the International Organization for the Study of IBD and recovered IBD patients with COVID-19 are registered at this secure site (https://covidibd.org), to help advance the understanding of disease progression.

Predisposition of COVID-19 patients to PD: There is increasing evidence documenting that PD pathogenesis may be modulated or even triggered by viral infections. This was exemplified in the epidemic of encephalitis lethargica following the 1918 H1N1 Spanish flu pandemic, almost all patients who had encephalitis lethargica developed post-encephalitis Parkinsonism, which clinically resembles PD (Dourmashkin 1997). Intranasal inoculation of H5N1 influenza virus into

mice induced microglia activation and neurotoxic aggregation of alpha-synuclein in brain regions infected by the virus. Histopathological examination of brain tissues revealed loss of dopaminergic neurons in the substantia nigra pars compacta and loss of striatal dopamine (Jang et al. 2009). It is known that dopaminergic neurons in the substantia nigra have lower levels of the glutathione antioxidant system, high bioenergetic demands and are selectively vulnerable to oxidative stress, and neuroinflammation. Viruses have evolved to hijack the host's cellular machinery to replicate efficiently and apply several strategies to disrupt cellular proteostasis pathways that may, in turn, lead to protein aggregation. It is possible SARS-CoV-2 might induce alpha-synuclein aggregation by blocking protein degradation pathways, similar to H1N1 influenza viral infection (Marreiros et al. 2020). Canonical PD neuropathologies are not only limited to influenza viruses but also associated with other neurotropic viruses, including West Nile virus, Japanese encephalitis virus, HIV, and human coronaviruses. The COVID-19 pandemic provides the scientific community an excellent opportunity to investigate the link between SARS-CoV-2 infection and neurodegeneration. We have recently summarized the possible mechanisms of neuroinvasion deployed by SARS-CoV-2 to gain entry into the brain and cause neurological injury (Alam et al. 2020).

There is a possibility that SARS-CoV-2 may also cause immunological injury and predispose infected individuals to PD in the future. New experimental evidence supports a role for the adaptive immune system, specifically T_H17 lymphocytes, in the pathogenesis of PD since increased numbers of T_H17 cells were detected in the peripheral blood of PD patients as compared to age-matched control subjects and also in postmortem midbrain (Sommer et al. 2018). T_H17 cells were able to induce dopaminergic neuron cell death in an autologous co-culture model of human induced pluripotent stem cell-derived dopaminergic neurons and T lymphocytes (Sommer et al. 2018). Furthermore, using neurotoxin-induced rodent models of

PD, it has been demonstrated that adoptive transfer of T_H17 cells into the midbrain resulted in increased IL-17 production, activation of microglia and dopaminergic neuron death, supporting the role of T_H17 cells in PD pathogenesis (Liu et al. 2019). A positive correlation between serum levels of IL-6 and IL-17 and severity of motor and non-motor symptoms were reported in a cohort of PD patients (Green et al. 2019). It is noteworthy that the severity of COVID-19 disease has been shown to positively correlate with IL-17 levels and related T_H17 cytokines, such as IL-1β, IL-6 and TNF-α that are known to promote vascular permeability and leakage, which could allow trafficking of T_H17 across the blood-brain barrier (Pacha et al. 2020). The question arises whether the presence of T_H17 lymphocytes and IL-17 in COVID-19 patients predispose them to develop PD, resulting in an increased future burden of PD. Indeed, PD is the fastest growing neurological disorder and with the world's population aging and now infected with COVID-19, the pandemic of PD is inevitable (G. B. D. Neurological Disorders Collaborator Group 2015).

Hallmarks of Aging and COVID-19: The process of aging is associated with modulation of immune responses, upregulation of chronic oxidative stress and production of pro-inflammatory cytokines (Pluvinage and Wyss-Coray 2020; Shaw et al. 2013). It is now well recognized that aging is associated with the presence of low-grade chronic inflammation termed as 'inflammaging' (Franceschi et al. 2000), and a decline in immune system function, referred to as 'immunosenescence'. Both inflammaging and immunosenesence negatively impacts the elderly. It is highly possible that these effects are further exacerbated in COVID-19 elderly patients as evidenced by unfavorable health outcomes and significant morbidity. Consistent increases in serum levels of IL-6 and TNF-α were found in the elderly (>65 yrs) individuals (Ferrucci et al. 2005), which can be further aggravated in COVID-19 patients leading to a hyperinflammatory responses. Elderly patients often display deficient adaptive immune responses, especially from T cells, and tend to be prone to enhanced innate immune responses (Chen et al. 2020a), both

of which, are thought to be important for development of severe COVID-19. Importantly, aging is also often associated with impaired cardiac and endothelial function (North and Sinclair 2012), which, coupled with the ability of the SARS-CoV-2 to target the endothelium, could explain the high levels of mortality in elderly populations.

The current landscape of COVID-19 therapeutics in Canada

Despite the serious public health challenges imposed by human SARS-CoV and MERS-CoV and more recently SARS-CoV-2, there is no vaccine, antiviral treatment or bio-therapeutic that has been approved for the treatment of these severe illnesses. There are over 1830 interventional clinical trials registered on ClinicalTrials.gov (ClinicalTrials.gov 2020) and, as of September 8th, 2020, 57 clinical trials have been authorized by Health Canada (2020). Any therapeutic, though, would take at least 12-18 months or years to obtain approval for human use. While we wait for the development of a vaccine or novel therapeutics, many pharmaceutical companies are repurposing therapies for the treatment of COVID-19 that are already approved by the FDA for other indications. This could be an efficient approach in rapidly bringing new therapeutic interventions for COVID-19 treatment. Though many therapeutics are currently in development (Table 3), these are covered extensively by previous reviews (Khan et al. 2020; Lundstrom 2020). For this reason, we will focus this section on therapeutics, especially biologics, that are being developed by Canadian companies and organizations and this information is current at the time of submission of this review.

***Prophylactic vaccines*:** Vancouver company Precision NanoSystems, in collaboration with CanSino Biologics Inc. from China, is working to develop a SARS-CoV-2 mRNA-lipid nanoparticle vaccine (Precision Nanosystems 2020). This technology relies on lipid nanoparticles to deliver *in vitro* synthesized RNA (Thomas et al. 2018), which would then self-

amplify within patient cells and express viral antigen to induce an immune-response. The National Research Council (NRC) Canada is collaborating with Variation Biotechnologies (VBI), an American company with a research facility in Ottawa, in developing a trivalent vaccine against SARS-CoV, MERS-CoV and SARS-CoV-2 spike proteins using VBI's enveloped virus-like particle (eVLP) technology (Kirchmeier et al. 2014; VBI 2020). The Edmonton based company Entos Pharmaceuticals is using its proteo-lipid vehicle technology to deliver a DNA based vaccine with the help of several international collaborators and plans to enter phase I/II clinical trials soon (Entos Pharmaceuticals 2020a). This technology utilizes viral proteins to mediate fusion between liposomes and cell membranes (Top et al. 2005). The University of Saskatchewan's Vaccine and Infectious Disease Organization-International Vaccine Centre is developing a subunit vaccine against COVID-19 (Provost 2020). This vaccine has recently cleared the preclinical stage, generating neutralizing antibodies and decreasing viral infection in ferrets, and will progress to human trials in the fall (Provost 2020). Another Canadian company located in Burnaby, Symvivo, is using their bacTRL platform, which uses the probiotic *Bifidobacterium longum* to replicate and deliver plasmids to cells in the gut (Symvivo 2020). These plasmids can then express protective nanobodies (Steeland et al. 2016) or viral proteins to induce short (via nanobodies) or long-term (via viral proteins) immunity by the host's adaptive immune system (Symvivo 2020). Currently, this bacTRL system using the SARS-CoV-2 spike protein is in phase 1 clinical trials (NCT04334980). A team from the University of Ottawa is seeking to develop a nasal spray vaccine using SARS-CoV-2 spike protein produced in plants (Sinclair 2020). Researchers at the Ottawa Hospital General Campus are hoping to repurpose their oncolytic vaccinia virus strains to construct a SARS-CoV-2 vaccine (Fleming 2020).

Although multiple novel platforms are being used for the development of vaccines against SARS-CoV-2, several challenges need to be overcome before a vaccine could become available for mass immunization. First, there is no consensus whether targeting the full-length or

only the receptor-binding domain of the virus's spike protein will produce optimal immune response. Second, concerns have been raised if vaccination with spike protein will either directly or as a result of antibody-dependent cell-mediated cytotoxicity exacerbate immunopathology in the lung. Third, whether a single-dose or multiple-doses of the vaccines will be needed to confer immunity, especially in the elderly as there is a significant age-related decline in the ability to mount an innate and adaptive immune response against vaccination (Poland et al. 2018). To date there are no FDA approved RNA vaccines, however they have advanced into human clinical trials and shown to elicit protective antigen-specific antibody- and T-cell mediated immune responses (Pardi et al. 2018). If an mRNA vaccine candidate against SARS-CoV-2 shows promising results it has the potential to rapidly clear regulatory hurdles.

Lastly, in the design of any vaccine, there is always the potential for generating antibodies that facilitate antibody-dependent enhancement (ADE) of infection. In fact, previous attempts at vaccination for other coronaviruses strategies have resulted in ADE responses that worsened disease and increased infection (32). Immune-mediated infections and ADE have long been known to be exploited by a variety of viruses such as dengue virus, HIV, and feline coronavirus (FCoV) as an alternative way to infect the host cell (Sullivan 2001; Takada and Kawaoka 2003). The safety profile of any such vaccine, or indeed the use of convalescent plasma, will also depend upon the minimization of antibody-dependent enhancement (ADE) of infection which can increase viral load and worsen infection. It is not currently known how much ADE contributes to COVID-19 but it is of critical importance for future vaccine development since an ideal vaccine candidate will exhibit neutralizing antibodies but minimize ADE. Human Fcγ receptor II (FcγRII) is the predominant receptor that mediates ADE infection by SARS-CoV and, in contrast to ACE2-mediated infection, is independent of endosomal or lysosomal pH and minimally affected by the activities of cysteine proteases (Jaume et al. 2011). Since many of

these *in vitro* studies utilized sub-neutralizing concentrations of recombinant antibody, this may not be the situation *in vivo* (Sharma 2020). To be clinically informative, studies must be done using COVID-19 patient serum that contains both neutralizing and ADE antibodies at relevant concentrations.

COVID-19 vaccines in human clinical trials: At the onset of the COVID-19 pandemic, investigators across Canada quickly transitioned to focus on COVID-19 research and joined the race to find safe and effective therapeutics. For example, IMV Inc. is a Nova Scotia-based company dedicated to the development of immunotherapies for cancers that has now deployed its platform for the development of a vaccine against COVID-19 and is planning to advance into human clinical trials (IMV Inc. 2020). A Quebec City based company, Medicago, has entered phase I clinical trials for its vaccine candidate, virus-like particles produced in plants (Medicago 2020).

***Antibody-based therapeutics*:** The University of Calgary and Sanofi-Aventis Canada Inc., whose head office is in Laval, are both testing the effects of monoclonal antibodies targeting IL-6, tocilizumab (Actemra) and sarilumab (Kevzara), respectively (Health Canada 2020). As discussed above, IL-6 is known to be an important indicator of severe disease and, given promising preliminary results of tocilizumab use in SARS-CoV-2 infected patients (Cellina et al. 2020; Xu et al. 2020b), its inhibition may prevent damage associated with hypercytokinemia. Two Canadian organizations, the C17 Council and Hamilton Health Sciences, are currently testing the feasibility of using convalescent plasma from patients who have recovered from SARS-CoV-2 infection to treat currently hospitalized SARS-CoV-2 patients (NCT04348656, NCT04377568). Some early studies suggest that convalescent plasma may be a safe and effective treatment for critical SARS-CoV-2 patients (Rajendran et al. 2020). A team at the University of Toronto is constructing synthetic antibodies to neutralize the virus (U of T News

2020). AbCellera, a Vancouver based company, has progressed to phase III clinical trials for its SARS-CoV-2 neutralizing antibody LY-CoV555 (AbCellera 2020). AbCellera is working in collaboration with the National Institute of Allergy and Infectious Diseases and the Eli Lilly and Company, both based in the United States. A nine lab team centered around University of Ottawa is planning to generate single-domain antibodies (also known as nanobodies) in llamas, which could be more efficient at coating and neutralizing virus than typical monoclonal antibodies (Sinclair 2020). A monoclonal antibody produced by the Markham, Ontario based company Edesa Biotech has gained approval to enter phase II/III clinical trials (Edesa Biotech 2020).

***Peptide and recombinant protein-based therapeutics*:** Toronto based Arch Biopartners has recently gained approval to conduct phase II clinical trials to test its anti-inflammatory peptide MetaBlok in SARS-CoV-2 infected patients (Global Newswire 2020). This peptide works by blocking a neutrophil adhesion receptor, reducing infiltration of neutrophils into lungs and liver (Arch Biopartners 2020; Choudhury et al. 2019). The University Health Network, Toronto are currently testing IFN-λ in phase II clinical trials (NCT04354259). IFN-λ has similar effects to the type 1 interferons IFN-α and β, but its function is more selectively tied to epithelial cells (Zanoni et al. 2017), limiting the more systemic side effects associated with type 1 interferon treatment. In a recent exploratory study that was a collaboration between multiple Canadian, Australian and Chinese groups, IFN- α2b has recently been found to reduce viral RNA and inflammatory markers (Zhou et al. 2020b). Interferon has previously been investigated for treatment of SARS, Ebola and Influenza (Konde et al. 2017; Loutfy et al. 2003; Nicholls et al. 2016). Exactis Innovation, a Montreal based company, along with several international collaborators, are testing to see whether degradation of NETs with recombinant human DNAse I in severe cases of CoVID-19 can reduce disease severity (NCT04409925). Currently, this treatment is in phase I clinical trials.

***Other biologics*:** A research team at the Ottawa Hospital Research Institute has recently been awarded a grant to study whether mesenchymal stromal cells from bone marrow or umbilical cord blood can limit inflammation and aid in repair of lung damage in SARS-CoV-2 patients with severe disease (Ottawa Hospital Research Institute 2020b). The Lawson Health Research Institute in London, Ontario is currently testing Bovine Lipid Extract Surfactant (BLES) in clinical trials for SARS-Cov-2 patients on mechanical ventilators (NCT04375735). Surfactant replacement therapy has previously been used to reduce mortality in pre-term infants with respiratory distress syndrome (Stockley et al. 2018), and it is hoped that it will improve outcomes for SARS-CoV-2 patients with severe disease. The Ottawa Hospital, with help from Canadian Cancer Trials Group at Queen's University and several other Canadian organizations, is testing the efficacy of heat killed bacteria to prevent and treat CoVID-19 in cancer patients (NCT04442048). This technology, called IMM-101, is being used to activate the innate immune system and protect patients against SARS-CoV-2 infection and is currently in phase III clinical trials (Ottawa Hospital Research Institute 2020a).

It is important to note that all of the above approaches are still in early stages of development and a significant amount of research will need to be done in the coming months to determine whether any of them will be effective to either prevent or treat COVID-19. It is still unknown whether any of these approaches are safe or effective, especially in Canada where the population is genetically, medically and geographically diverse. Finally, if a vaccine is developed, scale-up production, distribution and deployment will be a significant challenge, especially in areas with scarce medical facilities such as the northern territories.

Conclusions and future outlook

SARS-CoV-2 is a novel contagion in the human population, and despite our continued public health efforts over the past few decades, we have been caught off-guard by its tenacious spread across the world. As of the writing of this review, over 1 million people have died of COVID-19 worldwide and economies have shrunk by billions of dollars. Epidemiologists predict that more than half of the world population, over 3 billion people, will become infected with SARS-CoV-2 in the next year, possibly resulting in almost 1 million deaths by October, 2020 (Gu 2020; Taylor 2020). In Canada, anywhere between 1 and 4 million people could become infected with SARS-CoV-2, resulting in over 10 000 deaths (Gu 2020). Meanwhile, efforts to address this pandemic with robust and innovative scientific interventions continue. As SARS-CoV-2 continues to infect a rapidly-growing portion of the population we are learning a great deal about its biology, particularly how infection initiates and exacerbates COVID-19. Increasing evidence shows that COVID-19 is an inflammatory disease that in some patients resolves and in others results in hypercytokinemia and activation of coagulation pathways. Individuals with underlying chronic inflammatory diseases such as MS and arthritis are certainly at a disadvantage if they become infected with SARS-CoV-2. Elderly patients, particularly those in long-term care homes, who often have one or more of these underlying chronic conditions have been hardest hit by this disease in Canada. A dysfunctional immune response, associated with hyperinflammation and dampened adaptive immune responses have made this population particularly susceptible to infection by this virus. Although we have focused our efforts on the development of vaccines and therapeutics for COVID-19, research focused on understanding the human immune response to SARS-CoV-2, particularly in vulnerable populations, is necessary. In particular, we need to understand how this disease effects individuals with these chronic inflammatory diseases such as MS, PD and arthritis and how age influences immunity. Although not discussed in this review, children appear to be largely unaffected by SARS-CoV-2

infection and they appear to clear the virus without the systemic dysfunctions in inflammation observed in older adults (Cristiani et al. 2020). This could be an important gateway to understanding the vulnerabilities of SARS-CoV-2 and would give us important new tools to treat infections in older adults. Several powerful techniques could provide us with this type of large-scale population information. Systems biology –omics approach – integrating genomics, proteomics, lipidomics and metabolomics responses would be especially helpful in generating insight on a population-scale. This information will be necessary in predicting the efficacy and safety of a potential vaccine. This population-scale information will also be important in identifying pockets of the population that may have adverse reactions to specific interventions. With our ability to utilize machine learning and deep learning algorithms, we can generate 'molecular signatures' and create AI-enabled models of human immunity, all of which would be an incredibly powerful tools to predict how potential therapeutics would influence host responses and would accelerate vaccine and therapeutic development. As discussed in this review it is evident that based upon the immunopathogenesis of COVID-19, controlling the overt inflammatory response is equally important as targeting the virus.

Undeniably, SARS-CoV-2 will be with us for some time and it will challenge aspects of our medical, social and geopolitical fabric that we cannot fully anticipate. Within Canada, and as a member of the world research network, we must assemble and coordinate all of our scientific efforts to ensure that we address the needs of our vulnerable population in this current pandemic. And as we confront the current pandemic, we must also ensure that collective body of knowledge is preserved so that we can prepare for the next pandemic.

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Table 1. Characteristics of the most common *betaCoV*

Virus	Target receptors on host cells	Host cell	Reference
SARS-CoV	ACE2	Airway epithelia, lung parenchyma, vascular endothelia, kidney cells and small intestine	(Li et al. 2003)
	Unknown	Hepatocytes	(Hofmann et al. 2004)
MERS-CoV	DPP4	Lower respiratory tract, lung epithelial cells, kidney, small intestine, liver and macrophages	(Raj et al. 2013; Zhou et al. 2017)
SARS-CoV-2	ACE2	Airway epithelia, lung parenchyma, vascular endothelia, kidney cells and small intestine	(Hoffmann et al. 2020b; Zhou et al. 2020a)
	Integrins	Unknown	(Sigrist et al. 2020)
	NRP1	Respiratory and olfactory epithelium	(Cantuti-Castelvetri et al. 2020)
HCoV-OC43	HLA class I antigen	Unknown	(Collins 1993; Dijkman et al. 2013; Krempl et al. 1995; Vlasak et al. 1988)
	9-O-Ac-Sia	Unknown	(Krempl et al. 1995)
MHV	mCEACAM	Liver, epithelial cells of the intestinal and respiratory tracts, macrophages, neural cells and lymphocytes	(Nedellec et al. 1994; Williams et al. 1991)
PHEV	NCAM	Respiratory tract and central nervous system	(Mora-Diaz et al. 2019)
HCoV-HKU1	Unknown	Upper respiratory tract, lung epithelial cells	(Dijkman et al. 2013; Huang et al. 2015)

Abbreviations:

Virus: SARS-CoV- Severe acute respiratory syndrome coronavirus; MERS-CoV- Middle east respiratory syndrome coronavirus; SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2; HCoV-OC43- Human coronavirus OC43; MHV-Mouse hepatitis virus; PHEV-Porcine hemagglutinating encephalomyelitis coronavirus; HCoV-HKU1- Human coronavirus HKU1

Target receptor on host cell: ACE2- Angiotensin-converting enzyme 2; DPP4- Dipeptidyl peptidase 4; NRP1- Neuropilin-1; APN- Human aminopeptidase N; HLA class 1 antigen- human leukocyte antigen class I antigen; 9-O-Ac-Sia- 9-O-acetylated sialic acid; mCEACAM- murine Carcinoembryonic antigen-related cell adhesion molecules; NCAM- Neural cell adhesion molecule

Table 2. Clinical features of human infection by human *betaCoV*

Virus	Respiratory symptoms	Neurologic symptoms	Gastrointestinal symptoms	Reference
SARS-CoV	fever, chills/rigor, dry cough, sore throat, myalgia, dyspnea	Headache, dizziness, axonopathic polyneuropathy, myopathy, ischemic stroke	Watery diarrhea	(Bohmwald et al. 2018; Leung et al. 2003; Yeh et al. 2004)
MERS-CoV	Fever, myalgia, cough, dyspnea	Confusion, ataxia, focal motor deficit	Nausea, diarrhea, vomiting, abdominal pain	(Arabi et al. 2015; Assiri et al. 2013; Chan et al. 2015; Kim et al. 2017; Zaki et al. 2012)
SARS-CoV-2	Fever, dry cough, fatigue	Acute cerebrovascular diseases, impaired consciousness, skeletal muscle injury	Nausea, vomiting, loose bowel movement	(Guan et al. 2020; Holshue et al. 2020; Huang et al. 2020a; Mao et al. 2020; Wang et al. 2020b; Wong et al. 2020)
HCoV-HKU1	Fever, rhinorrhea, cough, dyspnea	Unknown	Diarrhea, vomiting, anorexia, nausea, abdominal pain	(Esper et al. 2006; Kanwar et al. 2017; Lau et al. 2006)
HCoV-OC43	Fever, cough, upper respiratory tract infection	Febrile seizures, Convulsions, Loss of consciousness, Encephalomyelitis Encephalitis	Diarrhea, emesis, abdominal pain	(Arbour et al. 2000; Gerna et al. 2006; Jean et al. 2013; Vabret et al. 2003; Yeh et al. 2004)

Table 3. Potential therapies for SARS-CoV, MERS-CoV and SARS-CoV-2

Target	Mechanism	Medication	Canadian Involvement	SARS-CoV	MERS-CoV	SARS-CoV-2	References
Host	Immune system activation	Interferons	Some trials	Effective *in vitro* and *in vivo*. Clinical results inconclusive.	Effective *in vitro* and *in vivo*. No effect on survival found in clinical studies.	Effective *in vitro*, Multiple clinical trials in progress	(Loutfy et al. 2003; Mo and Fisher 2016; Sallard et al. 2020; Stockman et al. 2006; Zhou et al. 2020b), NCT04354259
		IMM-101 heat killed bacteria	Yes	No info	No info	Currently in phase III clinical trials	NCT04442048
		Thymosin	No	No info	No info	Currently in clinical trials	(Liu et al. 2020c; Zhang et al. 2020d)
	Immunosuppression (Anti-IL6R)	Sarilumab	Some trials	No info	No info	Clinical trials in progress	NCT04341870,NCT04315298,NCT04327388,NCT04324073,NCT04345289,NCT04321993

		Tocilizumab	Some trials	No info	No info	Favourable clinical outcomes, several clinical trials in progress	(Alzghari and Acuna 2020; Cellina et al. 2020; Health Canada 2020; Xu et al.), NCT04347031,NCT04331808,NCT04322773,NCT04330638,NCT04315480,NCT04339712,NCT04333914,NCT04335305,NCT04310228,NCT04306705,NCT04332913,NCT04320615,NCT04335071,NCT04346355,NCT04332094,NCT04331795,NCT04345445,NCT04317092
	Immunosuppression	EB05	Yes	No info	No info	Approved for phase II/III clinical trials	(Edesa Biotech 2020)
		LSALT peptide	Yes	No info	No info	Currently in phase II clinical trials	(Arch Biopartners 2020 ; Global Newswire

							2020)
		rhDNase I	Yes	No info	No info	Currently in phase I clinical trials	NCT04409925
		Mesenchymal stromal cell transplant	Yes	No info	No info	Currently in clinical trials	(Ottawa Hospital Research Institute 2020b)
	VEGF-A Suppression	Bevacizumab	No	No info	No info	Currently in clinical trials	NCT04344782,NCT04305106,NCT04275414
Host & Virus	ACE2 mimic	rhACE2	No	No info	No info	Phase 1 clinical trials completed, phase 2 planned	NCT04335136
Virus	Fusion inhibition	019-nCoV-HR2P & EK1	No	No info	Effective *in vitro* and *in vivo*	Inhibition *in vitro*	(Xia et al. 2020; Xia et al. 2019)
		P9 peptide	No	Effective *in vitro* and *in vivo*	Effective *in vitro*	No info	(Zhao et al. 2016)
	Inhibition of viral entry, fusion or replication	Virus derived peptides	No	Inhibition *in vitro*	Inhibition *in vitro*	Inhibition *in vitro*	(Guan et al. 2020; Mustafa et al. 2018)
	Unknown	Mucroporin-M1 peptide	No	Inhibition *in vitro*	No info	No info	(Li et al. 2011)

	Vaccine	AdVac® Vaccine	No	No info	No info	Phase 1 clinical trials planned for September 2020	(Johnson & Johnson 2020)
		bacTRL-Spike Vaccine	Yes	No info	No info	In phase I clinical trial	NCT04334980
		ChAdOx1 nCoV-19	No	No info	No info	In phase 2/3 clinical trial	2020-001228-32
		Coronavirus like particles (CoVLP)	Yes	No info	No info	In phase I clinical trials	(Medicago 2020)
		DPX-COVID-19	Yes	No info	No info	In phase I clinical trial	(IMV Inc. 2020; Zhu et al. 2020)
		Enveloped virus-like particle (eVLP) vaccine	Collaboration	In development	In development	In development	(VBI)
		Fusogenix DNA vaccine	Collaboration	No info	No info	In development	(Entos Pharmaceuticals 2020b)
		mRNA-1273 Vaccine	No	No info	Currently at Research Stage	Phase 1 clinical trial in progress	NCT04283461
		Plant derived spike protein nasal spray	Yes	No info	No info	In development	(Sinclair 2020)

		Vaccinia virus vaccine	Yes	No info	No info	In development	(Fleming 2020)
		Various other vaccines	Some trials	Promising *in vivo* results, developm ent ceased	Protection found *in vivo*, currently several clinical trials	Several clinical trials in progress	(Enjuanes et al. 2008; Le et al. 2020; Rauch et al. 2018; Yong et al. 2019)
	Virus-targeted monoclonal antibodies	CR3022 monoclonal antibody	No	Effective *in vitro*	No info	Binding *in vitro*	(Tian et al. 2020)
		Single domain camelid antibody	Yes	No info	No info	In development	(Sinclair 2020)
		Various virus neutralizing monoclonal antibodies	Some collaborati on	Effective *in vivo*	Effective *in vivo*, in phase 1 clinical trials	Binding *in vitro*	(de Wit et al. 2018; Shanmugar aj 2020),NCT 03301090(Tian et al. 2020)
	Virus-targeted polyclonal antibodies	Covalescent plasma	Some trials	Improved outcomes clinically	Not tested	Positive clinical outcomes, multiple clinical trials in progress.	(Bleibtreu et al. 2019; Bloch et al. 2020; Mo and Fisher 2016), NCT04348 656, NCT04377 568

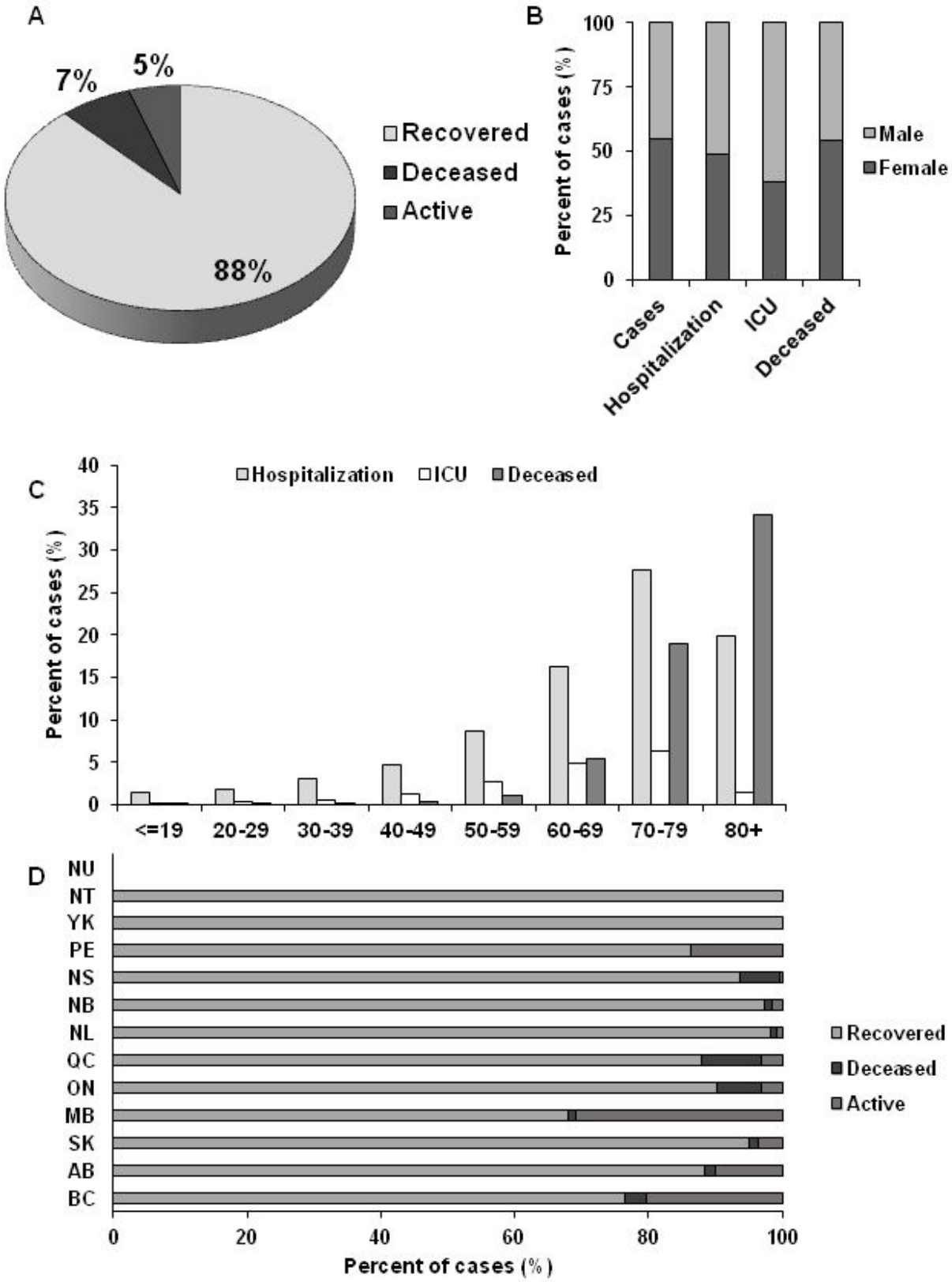

Figure 1. Demographics of COVID-19 in Canada. Data is based on https://health-

infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html accessed on September 8th, 2020 and is provided by the Government of Canada. (A) Proportion of cases in Canada that are recovered, deceased or active. (B) Proportion of cases of a given severity that were male and female. (C) Proportion of cases in Canada that result in hospitalization, ICU admittance or death in each age group. (D) Proportion of cases that are recovered, deceased or active in each province and territory. BC- British Columbia, AB- Alberta, SK-Saskatchewan, MB-Manitoba, ON-Ontario, QC-Quebec, NL-Newfoundland and Labrador, NB-New Brunswick, NS-Nova Scotia, PE-Prince Edward Island, YK-Yukon, NT- Northwest Territories, NU-Nunavut. Nunavut reports no confirmed cases.

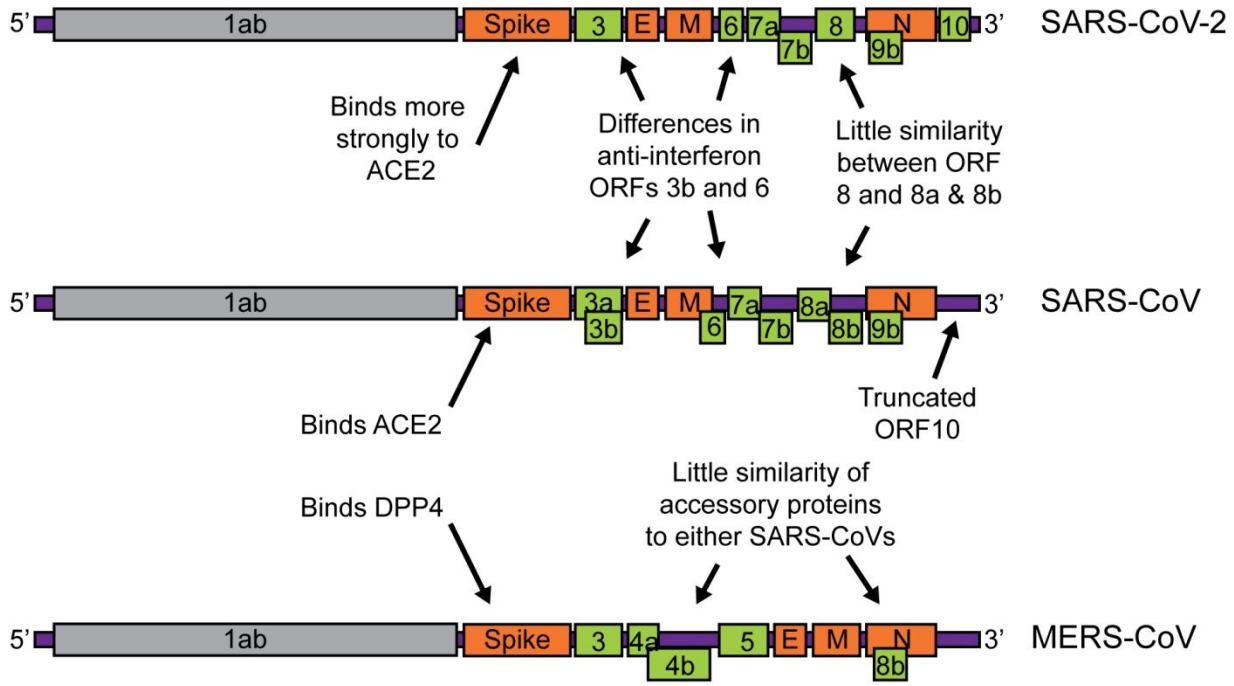

Figure 2: Schematic representation of the genomic organization of the three highly pathogenic human coronavirus genomes. The genome organization of SARS-CoV-2, SARS-COV and MERS-CoV is based on NCBI Reference Sequences NC_045512.2, NC_004718.3, and NC_019843.3. Non-structural ORF is shown in gray, structural ORFs are shown in orange, and accessory ORFs are shown in green. Coronaviruses contain a canonical set of four structural proteins: the spike glycoprotein (S), nucleocapsid protein (N), envelope protein (E) and membrane protein (M). The highly basic N proteins form a shell that encapsulates the genomic RNA to form a long, flexible nucleocapsid with helical symmetry. The nucleocapsid is surrounded by a lipoprotein envelope containing the S, E and M proteins (de Haan and Rottier 2005). In addition, the envelopes of some coronaviruses (e.g. porcine hemagglutinating

encephalomyelitis coronavirus) contain the hemagglutinin-esterase (HE) protein in their lipid envelope (Fung and Liu 2019).

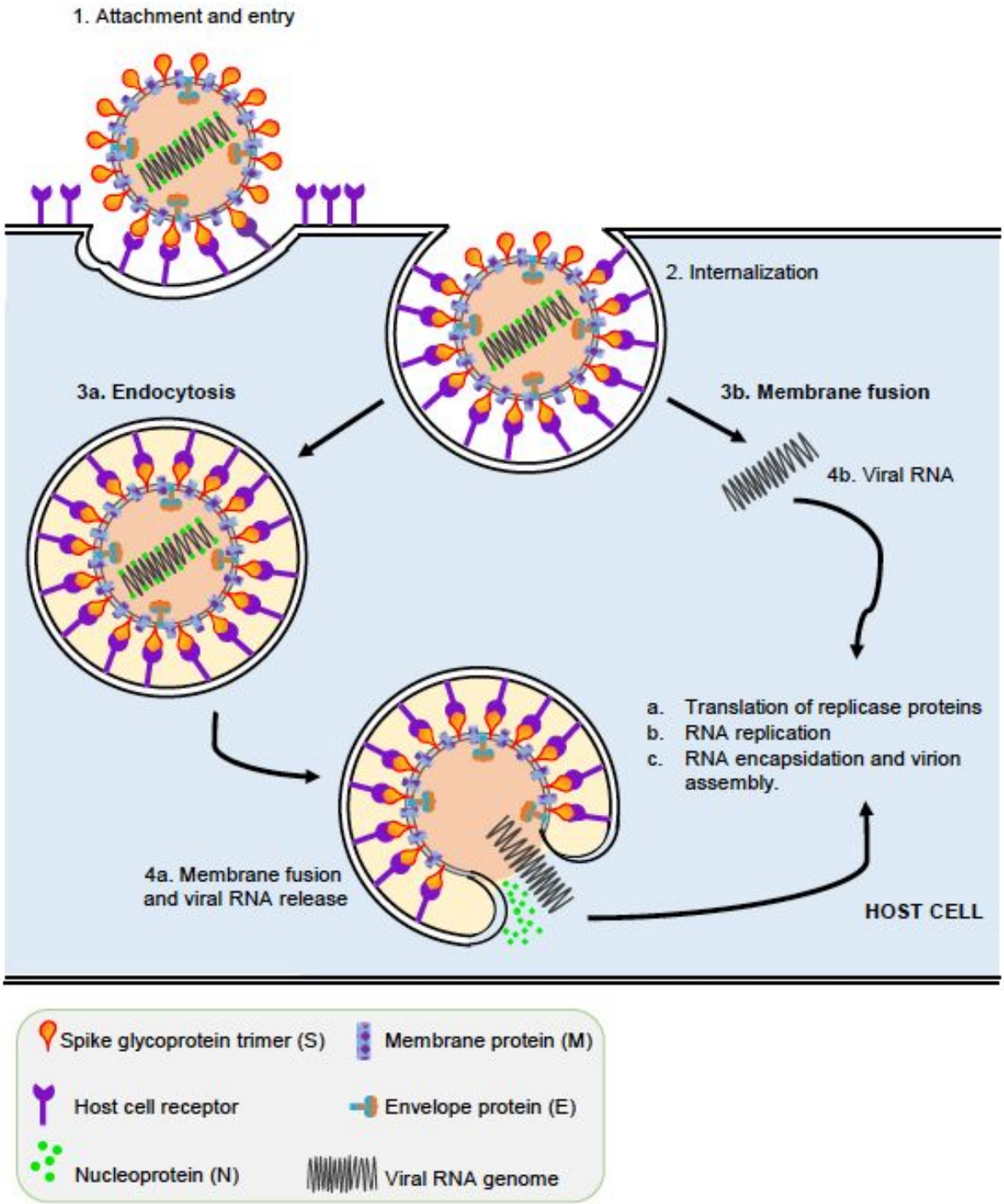

Figure 3. Schematic depiction of coronavirus entry into the host cells. (1) The virus attaches to the target host cell via interaction between the viral S protein and target cell receptor. The S protein, a type I membrane protein belonging to the class I fusion proteins (Bosch et al. 2003)

which has two functional subunits: the amino-terminal S1 subunit containing the receptor-binding domain and the carboxy-terminal S2 subunit that contains the domains required for membrane fusion. Once SARS-CoV-2 has bound to the host cell receptor via the S1 subunit, the TMPRSS2 protease primes viral entry into cells by initiating a cleavage at the S1/S2 junction (Hoffmann et al. 2020b). Notably, SARS-CoV-2 contains a furin-like cleavage site (Coutard et al. 2020), and cleavage by furin at the S1/S2 junction is important for entry into lung cells (Hoffmann et al. 2020a). The cleavage within the S protein by a cellular protease allows for the release of S2 subunit that causes fusion between the viral and cellular membrane (Hoffmann et al. 2020b). (2) The virions are internalized either by receptor mediated endocytosis (3a) or by membrane fusion (3b) (Burkard et al. 2014; Simmons et al. 2013) to release viral RNA (4b). The low pH of the endosomes causes membrane fusion between the viral envelope and endosomal membrane, followed by release of the RNA genome into the cytoplasm (4a). The viral RNA is utilized as a template by host ribosomes to translate into replicase proteins (5). The 3' terminus of the viral genomic RNA is polyadenylated and its 5' terminus is capped, allowing it to act as an mRNA for the translation of replicase polyproteins by utilising host ribosomes. This is followed by replication to produce multiple copies of progeny viral RNA as well as proteins (6). Progeny virions are produced by encapsidation and assembly of the newly synthesized viral RNA and viral proteins (7). The newly assembled progeny virions are released from the cells by budding.

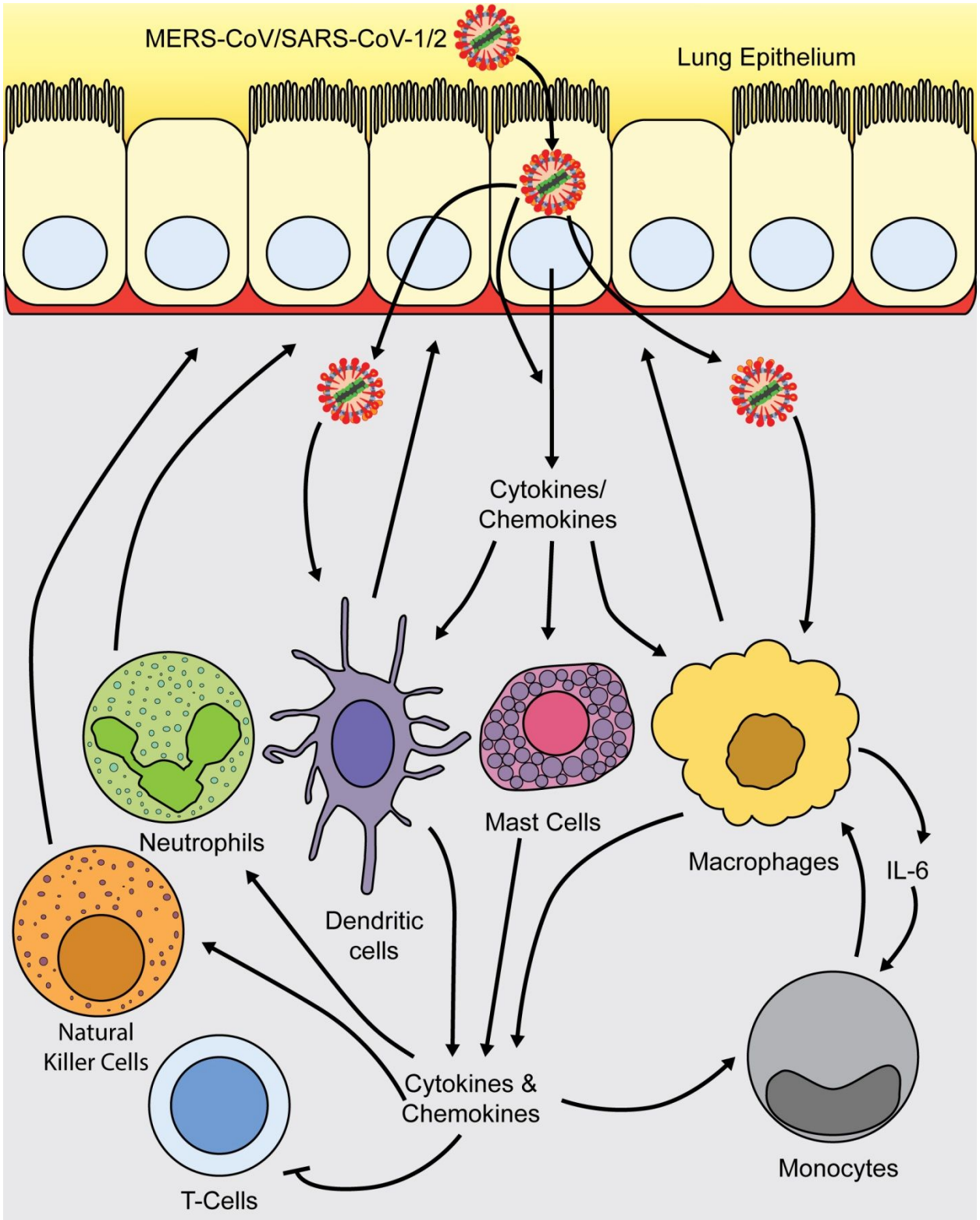

Figure 4. Schematic representation of the signaling pathways triggered by SARS-CoV-2 and induction of cytokine storm in the lung epithelium. SARS-CoV-2 binds to a specific receptor on lung epithelial cells leading to infection of lung epithelium. Virus then induces dendritic cells and monocytes to release interferons, cytokines and chemokines that attract and activate other inflammatory cells. This then leads to a vicious cycle of additional inflammation, as activated inflammatory cells release more pro-inflammatory cytokines. IL-6 seems to be particularly important, and is both released by macrophages and causes monocytes to differentiate into macrophages. Cytokines released by macrophages and dendritic cells can also inhibit T-cells.

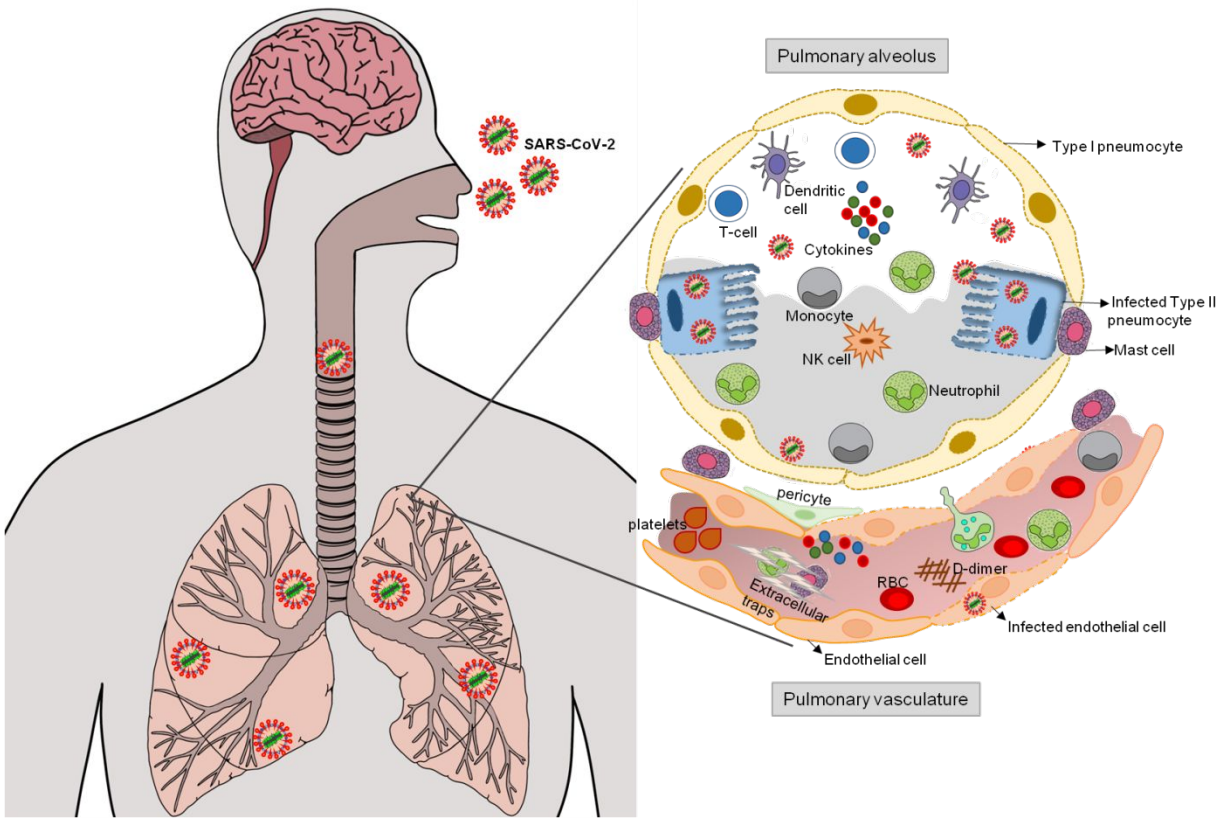

Figure 5. Schematic representation of inflammatory responses in the lungs of patients with severe COVID-19 disease. SARS-CoV-2 gains entry into the pulmonary alveoli where it infects and replicates in alveolar epithelial cells. Uncontrolled viral replication causes alveolar epithelial cell death and accumulation of cellular debris that elicits a pro-inflammatory response resulting in the generation of a robust “cytokine storm” by immune cells. The pro-inflammatory cytokines, in turn, further recruit more immune cells, such as neutrophils, monocytes and T-cells to the alveoli leading to a vicious cycle of inflammation. In conjunction, the virus spreads to the pulmonary vasculature where it infects endothelial cells accompanied with a massive production of pro-inflammatory cytokines, including IL-17 which induces the formation of extracellular traps of neutrophils and mast cells. These events lead to loss of vascular integrity, activation of coagulation pathways and inflammation that promotes the aggregation of platelets and fibrin to cause blood coagulation or thrombosis. Also, D-dimer (a protein fragment of dissolving blood clot), is elevated in the blood that is conventionally used as a biomarker of blood coagulation.

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