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SARS-CoV-2 in humans

SARS-CoV-2 beim Menschen

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Summary

The novel coronavirus SARS-CoV-2 became pandemic at the beginning of 2020, and caused about 80 million cases and more than 1.8 million deaths by the end of the year. As its relatives MERS- and SARS-CoV, but in contrast to the four human coronaviruses circulating worldwide, SARS-CoV-2 in a sizeable fraction of cases leads to a severe and potentially life-threatening disease, called COVID-19. Since in addition this virus is very contagious, particularly prior to onset or in absence of symptoms, and pre-existing immunity appears to be largely absent or at least of very little relevance, it is spreading rapidly in the population. A hallmark of COVID-19 is an at least partially detrimental immune response that not only can lead to serious lung damage, but may also damage organs outside the respiratory tract such as the heart and kidneys. This review summarizes current knowledge about the virus and the disease it causes, and outlines open questions in the different research fields.

Keywords: SARS-CoV-2, COVID-19, molecular biology, transmission, epidemiology, pathogenesis, treatment, immunity

Zusammenfassung

Das neuartige Coronavirus SARS-CoV-2 wurde Anfang 2020 zur Pandemie und verursachte bis Ende des Jahres etwa 80 Millionen Fälle und mehr als 1,8 Millionen Todesfälle. Wie seine Verwandten MERS- und SARS-CoV, aber im Gegensatz zu den weltweit zirkulierenden vier menschlichen Coronaviren, führt SARS-CoV-2 in einem beträchtlichen Teil der Fälle zu einer schweren und potenziell lebensbedrohlichen Krankheit: COVID-19. Da dieses Virus zudem schon vor Ausbruch bzw. auch ohne Symptome sehr ansteckend ist und möglicherweise vorexistierende Immunität sehr begrenzt zu sein scheint, breitet es sich in der Bevölkerung rasch aus. Ein Kennzeichen von COVID-19 ist eine zumindest teilweise fehlgeleitete Immunantwort, die nicht nur zu schweren Lungenschäden führen, sondern auch Organe außerhalb des Respirationstraktes wie Herz und Nieren schädigen kann. Dieser Übersichtsartikel fasst den aktuellen Wissensstand über das Virus und die von ihm verursachte Krankheit zusammen und skizziert offene Fragen in verschiedenen biomedizinischen Forschungsbereichen.

Stichwörter: SARS-CoV-2, COVID-19, Molekularbiologie, Übertragung, Epidemiologie, Pathogenese, Therapie, Immunität

Introduction

The first human Coronaviruses (hCoVs) have been isolated some 50 years ago from individuals suffering from mild respiratory infections. Four such "common cold" coronaviruses are known to circulate worldwide in humans, namely hCoV-NL63, -HKU1, -229E, and -OC43 (Almeida and Tyrrell 1967, Fehr and Perlman 2015, Masters and Perlman 2013). In stark contrast, two zoonotic coronaviruses infecting humans and capable of spreading in the human population have been described to cause severe to life-threatening diseases: severe acute respiratory syndrome coronavirus (SARS-CoV), first emerging in 2002 and rapidly spreading to several countries around the globe (covered in detail by A. Osterhaus in this volume); and middle-east respiratory syndrome coronavirus (MERS-CoV), first described in 2012 (covered in detail by Asisa Volz in this volume). While circulation of SARS-CoV could be successfully contained by globally implemented public health measures, cases of MERS-CoV infection are still regularly reported, mainly on the Arabian peninsula (World Health Organization 2020a).

In December 2019, cases of severe pneumonia of unknown – but likely infectious – etiology in the city of Wuhan, China, have been reported to the WHO (World Health Organization 2020c), which were shortly after linked to a newly isolated coronavirus, first termed 2019-nCoV (World Health Organization 2020b). Due to its high similarity to SARS-CoV, the virus was later renamed SARS-CoV-2. However, as highlighted in other articles within this volume, coronaviruses have been identified and isolated from a large range of other mammalian species, particularly bats. In fact, RaTG13, a coronavirus found in a horseshoe bat in Yunnan province, China, exhibits an even higher degree of similarity than SARS-CoV to the newly emerged SARS-CoV-2 with approximately 96% of sequence identity at the nucleotide level throughout most genomic regions. It therefore appears likely that SARS-CoV-2 originated from a zoonotic event, either directly from bat or via an intermediate host (Andersen et al. 2020; Boni et al. 2020). Backing this hypothesis, the virus' potential to readily cross species barriers was demonstrated by documented cases of SARS-CoV-2 transmission from humans to household animals (Shi et al. 2020; Sit et al. 2020) and from humans to farmed mink and back to humans (Oude Munnink et al. 2020). From lab experiments, it is known that particularly changes in the spike protein on the surface of the virions can lead to interspecies adaption in coronaviruses (Baric et al. 1997).

While the exact origin of SARS-CoV-2 still is under investigation, its impact on the human population has been dramatic. Since its first outbreak in Wuhan, it has spread with remarkable pace around the world, causing upwards of 80 million reported cases by the end of 2020, with more than 1.8 million deaths (World Health Organization 2021), and still raging. With SARS-CoV-2 and the associated coronavirus disease 2019 (COVID-19), human society thus faces a pandemic unbeknownst to living generations, with a broad spectrum of challenges for all disciplines of science. This article covers some of the key questions from the various branches of biomedical research.

Molecular biology of SARS-CoV-2 infection

Decades of research into the other coronaviruses have set the stage for fast progress in investigating SARS-CoV-2. As the general organization of the genes, detailed below, is conserved among all coronaviruses, SARS-CoV-2 was rapidly deciphered and viral protein coding genes were quickly defined. Furthermore, most aspects of the viral molecular lifecycle are shared with other coronaviruses (comprehensively reviewed in (V'Kovski et al. 2020)). As a plus-strand RNA virus, its genome constitutes a messenger RNA for the direct translation of viral proteins. Released from incoming virions into the cytosol right after cell entry, the viral genome serves as the message to produce viral proteins, which are translated as two long polypeptide precursors pp1a and pp1ab. The two polyproteins are then proteolytically cleaved by the viral cysteine proteases, non-structural protein nsp3 (PL^{pro}) and nsp5 ($3CL^{pro}$), giving rise to the 16 nsps of the virus. These provide a multitude of enzymatic activities required for viral genome replication and the modulation of host cellular processes. One essential enzymatic function not present in the human genome is the RNA-dependent RNA polymerase (RdRp), comprising nsp12, nsp8 and nsp7, which is also the target of the direct acting antiviral (DAA) remdesivir (Sheahan et al. 2020). The RdRP then, through negative-strand intermediates, generates copies of the full-length genomic RNA as well as eight species of subgenomic mRNAs (sgmRNAs). Those sgmRNAs code for structural proteins including nucleocapsid (N), spike (S), envelope (E) and membrane (M), as well as numerous auxiliary proteins. From other coronaviruses, in particular SARS-CoV, it is known that some of them antagonize host cellular antiviral defense pathways, most prominently the induction of and signaling by type I and III interferons (Park and Iwasaki 2020). Also, SARS-CoV-2 has been shown to encode an ample variety of activities targeting the host interferon and cytokine system (Hayn et al. 2020, Lei et al. 2020), believed to play a central role in dysregulating the immune response to infection and thereby crucially contributing to the development of COVID-19 (Acharya et al. 2020, Mathew et al. 2020, McKechnie and Blish 2020).

From the structural proteins together with genomic RNA, new virions are formed by budding into membranous structures at the interface between the endoplasmic reticulum (ER) and the Golgi apparatus, likely representing the ER-Golgi-intermediate compartment (ERGIC), coherent with previous reports on other coronaviruses (Cortese et al. 2020, Fehr and Perlman 2015, Masters and Perlman 2013). Offspring virus particles are then released through exocytic processes, not strictly requiring cell lysis.

Released viral particles will then infect neighboring cells. Again owing to the close similarity to related viruses, including SARS-CoV, angiotensin converting enzyme 2 (ACE2), which plays a major role in regulating electrolyte and fluid balance as well as blood pressure (Verano-Braga et al. 2020), was readily identified as the major receptor for cell entry (Hoffmann et al. 2020). Alternative entry receptors, such as CD147 or NRP1, are currently under discussion (Cantuti-Castelvetri et al. 2020, Daly et al. 2020, Shilts and Wright 2020, Wang et al. 2020a). It was further confirmed that the SARS-CoV-2

spike protein requires proteolytic processing ("priming") to mediate entry, and that this priming can be efficiently mediated by the cellular membrane-bound TMPRSS2 protease (Hoffmann et al. 2020). TMPRSS2 as well as further cellular proteases shown to play alternative or redundant roles, including furin and cathepsin L, can be pharmacologically targeted to prevent infection (Hoffmann et al. 2020, Pislar et al. 2020, Shang et al. 2020).

Transmission and epidemiology of SARS-CoV-2

In contrast to many animal coronaviruses, all known hCoVs primarily infect and replicate in cells of the respiratory tract, and SARS-CoV-2 is no exception in this regard (Fehr and Perlman 2015, Masters and Perlman 2013, Salzberger et al. 2020). In contrast to SARS-CoV, mostly replicating in epithelial cells of the lower respiratory tract, SARS-CoV-2 was found to infect and efficiently replicate also in cells of the upper respiratory tract, with nasopharyngeal and oropharyngeal swabs but also saliva containing high amounts of viral RNA and infectious virus (Cevik et al. 2020a, Wolfel et al. 2020, Wyllie et al. 2020). As a consequence, SARS-CoV-2 can easily transmit upon coughing, sneezing, singing and even talking. These activities produce a spray of droplets ranging from visible, large droplets, which will fall to the ground relatively quickly compared to microscopic (< 100 µM) (Prather et al. 2020) droplet nuclei lingering in the air as aerosols (Fennelly 2020, Klompas et al. 2020, van Doremalen et al. 2020). While transmission by larger droplets appears more prevalent, long distance transmission by aerosols may, at least in part, explain so-called "superspreading events", in which a small number of index patients, or even only a single infected person, transmit the virus to large numbers of people in the same confined space (Cevik et al. 2020a), for example in large open-plan offices (Park et al. 2020b), festivities (Ghinai et al. 2020), churches (James et al. 2020), meat processing facilities (Guenther et al. 2020) or choirs (Hamner et al. 2020). Similar to SARS-CoV, but different from most seasonal respiratory viral infections, the higher propensity of SARS-CoV-2 to transmit via such one-to-many "superspreading events" needs to be taken into account for epidemiological modelling. The number of secondary cases caused by single patients is generally very low, between zero and one for most patients, but follows a negative binomial distribution with a very long tail, corresponding to an average R0 between 2 and 3 with a small (much less than 1) dispersion parameter (Adam et al. 2020, Althouse et al. 2020, Kupferschmidt 2020, Li et al. 2020a, Liu et al. 2020b, Park et al. 2020a).

Another feature of SARS-CoV-2 transmission is presymptomatic contagiousness, and possibly transmission by infectees who remain fully asymptomatic. While the extent of the contribution of truly asymptomatic carriers to the overall epidemiology of SARS-CoV-2 is still debated, transmission one to two days prior to the onset of symptoms likely plays a decisive role in rapid community spread (Cevik et al. 2020a, Kasper et al. 2020). In general, transmissibility is highest around the onset of symptoms and quickly declining thereafter (Cevik et al. 2020b).

Taking those basic epidemiological characteristics into account, policy responses at the beginning of the pandemic early on prohibited large gatherings and especially indoor events with large numbers of attendees, and in a second step, many countries promoted the use of face masks to curb virus spread (Flaxman et al. 2020). By and large, these public health measures were shown to be actually effective (Chu et al. 2020, Dehning et al. 2020). However, epidemiological analyses are still ongoing, as the situation is highly complex and differs between regions, countries and continents. In general, human respiratory viruses and in particular the endemic hCoVs exhibit clear seasonal profiles (Moriyama et al. 2020). In fact, Europe experienced a low-incidence situation throughout summer, but suffered from steeply increasing case numbers from September/October on, reaching multiples of the numbers recorded in spring (Cacciapaglia et al. 2020, European Centre for Disease Prevention and Control 2020, Looi 2020).

The use of high-throughput RNA sequencing to determine the entire sequence of patient isolates, although varying between countries, has identified a myriad of sequence variants, which are deposited and available through database platforms such as NextStrain (Hadfield et al. 2018). Phylogenetic analyses of viral sequences enable close tracking of the mutational course of the virus. This not only permits the precise reconstruction of transmission chains and epidemiologic events (Popa et al. 2020), but also allows for worldwide monitoring of the genomic landscape of SARS-CoV-2 and the identification of mutations that got fixed in the viral genome. Mutations within the S protein of circulating viruses are particularly in focus, as it is both the major determinant for efficient cell entry and the major antigen for neutralizing antibody responses. Also mutations in other parts of the genome might confer increased virulence. Of note, coronaviruses generally have relatively low mutation rates as they uniquely bear a proofreading replication mechanism, likely due to their genomes being amongst the largest (~30,000 bases) of all RNA viruses (Fehr and Perlman 2015, Masters and Perlman 2013).

An early spike protein mutation, D614G, emerged within the first weeks of the pandemic and quickly took over (Korber et al. 2020). In fact, it could be demonstrated that the D614G variant shifts the S protein conformation towards higher ACE2-binding and fusogenicity, leading to increased infectivity of the virus ***in vitro*** (Korber et al. 2020, Yurkovetskiy et al. 2020). Recently, it was confirmed that also ***in vivo*** transmissibility in animal models was significantly enhanced in the D614G variant, however, pathogenicity was not (Hou et al. 2020a). In December 2020, a new variant (B1.1.7) bearing several mutations in the S protein was identified in the United Kingdom, which was spreading rapidly, again indicating significantly higher transmissibility (Davies et al. 2020).

Clinical characteristics of COVID-19

Respiratory viruses are very common. Rhinoviruses, adenoviruses, respiratory syncytial viruses and of course influenza- and coronaviruses, cause a range of illnesses, including the very frequent common cold. SARS-CoV-2 was initially described to cause severe viral pneumonia, resembling the clinical picture of SARS and MERS, displaying typical ground-glass-opacities in chest radiography and leading to acute respiratory distress syndrome (ARDS) in a sizeable proportion of patients (Huang et al.

2020). As sensitive and specific molecular testing became more readily available (Corman et al. 2020), it was found that SARS-CoV-2 infection in fact presents a broad outcome, from asymptomatic to life-threatening (Docherty et al. 2020). Whereas initially up to four out of five infections were thought to occur with no or very mild symptoms (Keeley et al. 2020), this number dropped to currently about one in six (Cevik et al. 2021). Approximately 20% of cases require hospitalization (Kasper et al. 2020, Pollan et al. 2020), 5–10% are admitted to intensive care (Phua et al. 2020) and 0.1%–2% are dying. This "infection fatality rate" shows substantial variation between different reports, which could be due to underlying, e.g. geographical or social, differences (Levin et al. 2020, O'Driscoll et al. 2020, Pastor-Barriuso et al, 2020, Stadlbauer et al. 2020). Severity of the disease, and in particular mortality increases significantly with male sex and drastically with the infectee's age, reaching infection fatality rates of up to 10% in those aged above 80 (O'Driscoll 2020). Besides sex and age, pre-existing conditions strongly affect the risk of severe COVD-19, including hypertension, cardiovascular disease, COPD and diabetes (Cevik et al. 2020a, Cevik et al. 2020b, Liang et al. 2020, Trump et al. 2020, Williamson et al. 2020). Apart from severe acute disease and death, even for less severe course of COVID-19, long-term complications such as fatigue, impaired physical fitness, or mental health probles, are receiving increasing attention (Carfi et al. 2020, Huang et al. 2021, Mitrani et al. 2020, Nature Medicine Editorial 2020). Such long-term effects are also known to occur following influenza infections (Wang et al. 2020b), however causes and virus-specific aspects remain to be elucidated.

Among the most frequently reported symptoms of SARS-CoV-2 infection are headache, non-productive cough and a unique impairment of the sense of smell and taste (Kasper et al. 2020, Makaronidis et al. 2020). In contrast to initial reports, which were somewhat biased towards hospitalized cases, fever is reported in a significantly smaller fraction of cases (Kasper et al. 2020). In more severe courses of COVID-19, these initial, flu-like symptoms are then followed by generalized weakness, chest pressure or pain and a shortness of breath (Hall et al. 2020). Although classical signs of atypical pneumonia can already be appreciated in chest radiography, the general condition of the patient may remain stable, with acute pulmonary symptoms going along with a rapid decline in oxygen saturation only setting in with significant delay (Herrmann et al. 2020, Rubin et al. 2020, Tobin et al. 2020). A sizeable fraction of patients requiring intensive care deteriorate significantly developing ARDS and requiring mechanical ventilation or even extracorporeal membrane oxygenation (ECMO), which is the only life-saving measure left in the most critical cases (Barbaro et al. 2020). Still, respiratory failure due to ARDS is the leading cause of COVID-19 related deaths, accounting for approximately 70% of fatal cases (Zhang et al. 2020a).

An increasing body of literature further suggests other organs in the human body to be affected. In particular the loss of smell and taste was speculated to be due to direct viral infection of cells of the olfactory system (Bilinska and Butowt 2020, Butowt and von Bartheld 2020, Meinhardt et al. 2020). Further reported extra-pulmonary manifestations of COVID-19 include (but are not limited to) diarrhea, gastrointestinal and liver injury (Lamers et al. 2020, Zhong et al. 2020), myocarditis (Puntmann et al. 2020), renal failure (Gabarre et al. 2020) as well as severe endothelial damage and increased blood clotting (Perico et al. 2021). Whether those symptoms are caused by direct viral infections is still under investigation. ACE2, the main entry receptor for SARS-CoV-2, is expressed on cells of various organs (Ziegler et al. 2020). Indeed, ***in vitro*** infections were efficient on a range of models including cardiomyocytes, brain organoids, pancreatic cells, gut and liver organoids to name a few (Yang et al. 2020a). However, presence of infectious viral particles in the bloodstream would be assumed to be required for infection of distal organs, but is only scarcely detected (Walsh et al. 2020).

COVID-19 pathogenesis and treatment options

The pathomechanisms underlying this very broad spectrum of symptoms are only begun to be understood. An emerging general view is that the disease proceeds in two phases (Li et al. 2020b, Tay et al. 2020). In the first phase, the virus infects and replicates in epithelial cells of the upper respiratory tract. It then spreads and descends until it reaches cells in the lung, likely alveolar epithelial cells. During this phase, viral infection induces innate immune responses, recruiting macrophages and monocytes, but also cytotoxic cells to the sites of infection. It is likely that in the majority of patients suffering no or only mild symptoms, this regular immune response is sufficient to effectively control the virus.

However, in moderate to critical courses of the disease, a second phase with potentially life-threatening consequences initiates. The currently prevalent hypothesis focuses on the hyperactivation of immune cells and a massive secretion of cytokines, sometimes termed "cytokine storm" (Li et al. 2020b, Mangalmurti and Hunter 2020, Moore and June 2020, Tay et al. 2020). Albeit not fully understood, it appears likely that following infection, the cellular response is shifted away from antiviral interferons towards pro-inflammatory cytokine secretion (Acharya et al. 2020, Galani et al. 2021, Neufeldt et al. 2020).

Broadly speaking, the research on the causes of severe COVID-19 can be divided in two areas. First, there is the question of where and how does this detrimental response to the infection initiates. Second, factors that contain or amplify and worsen the outcome shall be identified.

To answer the first question, experiments are conducted in a range of model systems and combined with data from patient samples. An important limitation for the latter is that due to the lag time from infection to symptom onset and hospitalization, early stages of the infection cannot be monitored.

Initial studies in cell culture showed an induction of pro-inflammatory genes in virus-infected epithelial cells (Blanco-Melo 2020), however, as for interferon genes, only in small subsets of cells (Fiege et al. 2020, Wyler et al. 2020). Data from bronchoalveolar lavages (Liao et al. 2020), ***ex vivo*** infected human lung tissue (Hönzke et al. 2020) or Syrian hamsters (Nouailles et al. 2020) indicate that, at least in the lower airways, infection of epithelial cells is neither particularly efficient, likely also due to low levels of ACE2 expression (Hönzke et al. 2020, Hou et al. 2020b), nor elicits a strong transcriptional response. However, these studies support an important role for macrophages in triggering a potentially excessive pro-inflammatory response. Along these lines, macrophages

in samples from upper airways showed higher expression of pro-inflammatory cytokines in patients with critical compared to moderate COVID-19 (Chua et al. 2020). Infiltration of lung alveolae by myeloid cells, particularly neutrophils (Potey et al. 2019), along with interstitial liquid, then leads to a significant impairment of the respiratory capacity and, hence, ARDS. The strong increase of inflammatory cytokines such as interleukin 6 or tumor necrosis factor (TNF) may constitute an important factor for observed manifestations at distal sites, such as damage to blood vessels or the kidney and increased blood clotting (Acharya et al. 2020, Mangalmurti and Hunter 2020, Perico et al. 2021, Tay et al. 2020).

A range of aspects potentially modulating the grade of the disease are currently investigated. In one study, impaired interferon type I response was observed in severe and critical COVID-19 patients (Hadjadj et al. 2020). However, other reports presented different conclusions (Lee and Shin 2020), and a large clinical trial did not find a positive effect for the proposed treatment of COVID-19 using interferons (Consortium et al. 2020). Still, this topic will likely remain a focus, since loss-of-function polymorphisms of interferon inducing pathways and autoantibodies against type I interferons were found to be important risk factors (Bastard et al. 2020, Zhang et al. 2020b). With regard to the humoral immune response, both specific temporal profiles (Lucas et al. 2020, Zohar et al. 2020) and sugar modifications of antibodies (Chakraborty et al. 2021, Larsen et al. 2020) have been connected to disease severity. Furthermore, genome-wide association studies identified specific alleles of several genes to be significantly linked to the course of the disease (Pairo-Castineira et al. 2020, Severe Covid et al. 2020). Finally, the role of immune cells in the peripheral blood is under intense scrutiny. Different subtypes were found to be deregulated, which could also serve as prognostic markers (Chua et al. 2020, Mathew et al. 2020, Schulte-Schrepping et al. 2020, Silvin et al. 2020).

Consistent with the notion of an important role of pro-inflammatory signals in COVID-19, the immune modulatory corticosteroid dexamethasone was shown to benefit patients (Stratton et al. 2020) suffering from severe/critical disease, as were – to certain extents – the JAK/STAT inhibitor baricitinib (Kalil et al. 2020) and the IL-6 receptor antagonist tocilizumab (RECOVERY Collaborative Group et al. 2021). In further support of the notion of immune- rather than direct virus-driven pathology, compounds directly interfering with viral replication, in particular the initially promising viral RdRP inhibitor remdesivir, were tested in several trials, but eventually provided only weak support for regular use (Beigel et al. 2020, Consortium et al. 2020). Virus-directed therapeutic antibodies however showed more promising results in that they were able to reduce viral load (Chen et al. 2021, Weinreich et al. 2021).

Immunity to SARS-CoV-2

For the four common cold hCoVs, current knowledge indicates that immunity is often partial and might not last longer than several months to a few years (Edridge et al. 2020). However, due to their widespread circulation, through recurrent infections antibody serum levels can remain elevated (Edridge et al. 2020). It has been proposed that a certain degree of immunity may be cross-protective between the different endemic hCoVs and in fact, a small percentage of SARS-CoV-2-naïve sera contained anti-hCoV-IgG capable of neutralizing SARS-CoV-2 (Ng et al. 2020). Along these lines, a certain cross-reactivity was also shown on the level of memory B cells (Sokal et al. 2021). A stronger and putatively longer lasting effect was seen in T-cell responses, where circulating T-lymphocytes specific to epitopes of endemic hCoVs proved to be cross-reactive to epitopes of SARS-CoV-2 (Braun et al. 2020, Le Bert et al. 2020, Mateus et al. 2020). Of note, these studies have shown cross-reactivity, however, it remains to be investigated if these responses would be protective (de Vries 2020), and even if so, it may not have substantial impact on the current epidemiological understanding of the pandemic (Lipsitch et al. 2020).

Whereas pre-existing immunity, as described above, likely has a very limited impact, a large majority of people infected with SARS-CoV-2 rapidly develops a robust and specific antibody and memory B cell response (Guo et al. 2020, Long et al. 2020, Okba et al. 2020, Sokal et al. 2021), with IgA dominating the early neutralizing activity (Sterlin et al. 2020). The induction of humoral immunity may depend on the severity of the disease (Roltgen et al. 2020), however, strong immune response were reported across all disease severities. Some reports indicate a rather quick waning of circulating antibodies (Bruni et al. 2020, Roltgen et al. 2020, Seow et al. 2020), whereas others suggest that protective antibody titers may remain robustly elevated at least for five months (Gudbjartsson et al. 2020, Wajnberg et al. 2020), and B-cell memory likely persists for even longer (Rodda et al. 2020, Sokal et al. 2020). Treatment of severe COVD-19 cases with plasma of convalescent patients has been proposed and clinically tested, but yielded mixed results (Liu et al. 2020a, Rojas et al. 2020, Simonovich et al. 2020).

Beside antibody responses, also T-cell immunity is induced upon infection with SARS-CoV-2 (Cox and Brokstad 2020). While T-cells may contribute to immunopathology in COVID-19 (Gustine and Jones 2021, Mathew et al. 2020, Yang et al. 2020b), they may also play an important role in controlling the infection and, possibly, mediating long-term protection (Chen and John Wherry 2020, Cox and Brokstad 2020, Le Bert et al. 2020, Rydyznski Moderbacher et al. 2020). As it is difficult to functionally relate reactivity to actual protection, the contributions of CD4+ and CD8+ T-lymphocytes requires further investigation. Understanding their role in COVID-19 better, should further direct the development of vaccine candidates.

Owing to the unprecedented importance of controlling this novel viral threat, more than 180 vaccine candidates are currently under development [(Krammer 2020); see also the article by M. Bastian in this volume]. Preliminary reports were insofar promising as they report very strong immune responses across a range of vaccine types (Folegatti et al. 2020, Jackson et al. 2020, Keech et al. 2020, Krammer 2020, Mulligan et al. 2020, Zhu et al. 2020). Two vaccines, both first-of-their-kind mRNA-based approaches (Baden et al. 2020, Polack et al. 2020), and two adenovirus-vectored vaccine candidates showed efficacies in phase 3 clinical studies ranging up to about 90% (Logunov et al. 2020, Voysey et al. 2020). Around the globe, more and more vaccines with different methodologies (including inactivated viruses and purified antigens) are being established and approved. Broad vaccinations that likely offer a high degree of protection at least for a limited period of time, thus, appear to be in feasible reach. If necessary, regular overhauls of the vaccines due to a mutating

virus, somewhat akin to the current influenza vaccination approach, is quickly possible at least with non-vectored vaccines and opens the chance for sustained control of the SARS-CoV-2 pandemic.

Summary and outlook

The year 2020 has not only seen a rapid spread of the novel coronavirus SARS-CoV-2, but also a massive and worldwide effort in all fields of biomedical research and beyond. Owing to substantial progress in elucidating the basic biology of virus infection and the molecular pathogenesis of severe COVID-19, possible paths to reliable treatments are only slowly clearing up. In contrast, a broad range of vaccines shown to be safe and efficacious were developed and approved with unprecedented speed. Challenges for the months and years to come include, among others, the elucidation of the frequency, causes and severity of long-term health impairments, and to translate the accumulating knowledge about SARS-CoV-2 biology into therapeutic strategies. With the prospect of a quickly increasing share of the world's population being vaccinated, the surveillance of possibly emerging vaccine-resistant mutants will further be essential for a sustainable control of SARS-CoV-2.

Ethical Approval

Not applicable.

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Conflict of interest

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Authors contribution

Both authors equally contributed to literature searches and text writing.

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