NOVEL HUMAN PATHOGENIC CORONAVIRUS: SARS-CoV-2

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The new human coronavirus that emerged in Wuhan, Central China, in December 2019, has been named SARS-CoV-2 by the International Coronavirus Study Group. This coronavirus (CoV) that has already been extended to 171 countries, has a sequence identity higher than 80% with the SARS-CoV that emerged in Guandong province of South East China in 2002. This novel virus SARS-CoV-2 is causing a pandemic, certainly the most important one in the recent decades, as it has already affected 491,623 people (as of March 26th, 2020; source: John Hopkins University, Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering), of which 22,169 have died in around four months. During the first phase of the pandemic 80% of these cases (81,054) took place in China, but now European countries, especially Italy, Spain and Germany, and also USA and Iran, are taking the lead in the list of new infected people per day.

SARS-CoV-2 causes a mild pathology in 80% of infected patients, 14% develop severe disease, and 6% become critically ill. The virus may cause pneumonia associated with fever, headache, and respiratory difficulty, that may evolve to exacerbated lung inflammation, edema and death in around 2% of infected patients. Older adults, particularly those that have associated additional pathologies, such as diabetes, cardiovascular disease or additional respiratory complications, are more susceptible of having a drastic outcome, although younger persons with ages above 35 years, sporadically also have a negative outcome.

At present, seven coronaviruses infecting human beings are known. Four of them cause a midwinter common cold, and almost all adults have already been infected by one or more of them. In contrast, the other three human coronaviruses (that is SARS-CoV that emerged in the South East of China in 2002, MERS-CoV that emerged in the Arabian Peninsula in 2012, and the recently emerged SARS-CoV-2 that was identified for the first time in Wuhan) caused the death in 10%, 35% and around 2% of the infected people, respectively. The three deadly coronaviruses for humans have affected for the moment to 8,000, 2,600 and 491,623 confirmed patients, respectively, showing that they have had a high impact in human population, particularly the SARS-CoV-2. Nevertheless, epidemiologists consider that the real number of infected persons is several folds higher.

During their replication, RNA viruses introduce mistakes into their genome (around one for each 10,000 nucleotides added), leading to the generation of a huge amount of new virus mutants, some of them able to cross species barrier and infect humans. Most likely this has caused the epidemic outbreak at the end of 2019. Unfortunately, in this epidemic the vector that has served as an intermediate vehicle amplifying the virus before being transmitted from bats to humans has not been identified. In fact, although games, snakes and pangolins have been suggested as the intermediate host, the scientific evidence provided has not been considered solid. Based on previous experience on coronaviruses crossing species barriers, and on viral genome sequence data, it has been postulated that an intermediate vector between bats and humans, most likely another mammal, has passed the virus. This statement is based on the observation that although there are many SARS-CoV-like viruses in bats, their genome sequence identity with the new Wuhan virus is lower than 96%, and it would have been needed the reiterated growth of this virus through an intermediate vector to evolve their sequence to that of SARS-CoV-2. The direct jump of a virus from bats to humans is considered unlikely, because in December of 2019 bats were in their hibernation period in the Wuhan area, and because the known sequences of bat coronaviruses are still significantly different from that of the SARS-CoV-2.

A behavior of the Wuhan coronavirus which makes the control of this epidemic harder, is that a large proportion of the infected patients undergo a long incubation period that normally ranges from 2 to 14 days (exceptionally up to 28 days), without showing clinical signs of disease, facilitating the dissemination of the virus. In addition, 14% of the infected persons, after recovery and being declared free of the virus, apparently become again positive in the polymerase chain reaction (PCR) that amplifies the viral genome. An explanation for the apparent reappearance of SARS-CoV-2 in some patients, which is getting higher support, is that the apparently cured patients did not fully cleaned all the virus from their bodies. In fact, as a precaution it has been suggested testing recovered patients at intervals of seven, 14 and 21 days after being considered clean, using similar biological samples. The seeming reappearance of the virus could also have been possible if the virus would have antigenically evolved in order to evade the immune response; this seems unlikely in view of the high virus sequence conservation, particularly in the domains of the S protein eliciting neutralizing antibodies. An alternative possibility postulated is the induction by the virus of a relatively weak immune response. The generation of a humoral immune response by SARS-CoV-2 has been demonstrated in macaques, what justifies the recovery of the majority of the patients. However, more detailed studies on the humoral and cellular responses elicited by the Wuhan virus are urgently needed, and also the identification of viral genes that may suppress the immune response induced by SARS-CoV-2.

On the positive side, diagnostic kits based on PCR which allow to specifically determine SARS-CoV-2 nucleic acid presence within 3-4 hours have been developed, thanks to the prompt release of virus sequence by Chinese scientist. Furthermore, kits based on serological analysis providing a reply in 15 minutes are already in place.

Nowadays, more than 60 CoV treatments are in development, including antivirals, antibodies and vaccines. In fact, a collection of antivirals is already being tested in clinical trials. Among those marketed by strong multinational companies, one heading the race is Remdesivir developed by Gilead. Another treatment in the top category is AbbVie's Kaletra, also marketed as Aluvia, (Lopinavir/Ritonavir), which received a low level report on March 21st, 2020. More recently Favipiravir, marketed by Fujifilm as Avigan, among others has emerged as a new candidate. Another promising antiviral under study, with a well found scientific bases is Aplidin, which inhibits the growth of human CoV in infected cells at nanomolar concentrations. This antiviral is moving to clinical trials, launched by Pharmamar (Spain).

In terms of vaccines, there are many potential types, including those based: (i) on a single viral protein, preferentially the Spike (S) protein of the virus or the S1 subunit (globular domain, including the receptor binding site) of the novel coronavirus in combination with an adjuvant; (ii) on the expression of S protein using already developed viral vectors such as adenovirus 5, the Chinese vaccine that seems one of the most advanced ones; (iii) on Moderna's company and the NIAID headed by Antony Fauci, based on a messenger RNA coding for S protein (mRNA-1273); (iv) on MVA poxvirus vectors expressing S protein under development by Mariano Esteban's laboratory at the National Center of Biotechnology (CNB-CSIC, Madrid).

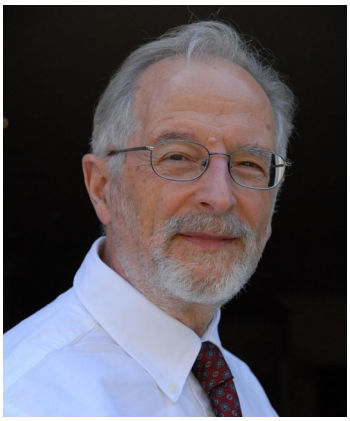
Alternatively, in our laboratory of the CNB-CSIC we are constructing SARS-CoV-2 RNAs as vaccine candidates. These RNAs encoding the viral antigen elicited a protective immune response. Our laboratory has constructed a full-length copy of the SARS-CoV-2 genome. Development of this vaccine candidate is based on previously engineered vaccines for SARS- and MERS-CoVs that provided 100% protection in experimental animal models (humanized transgenic mice) and are ready for their evaluation in clinical trials.

The number of new SARS-CoV-2 cases in China has been constantly decreasing and as of March 22st, 2020, only imported cases are being reported. On the other side, it is clear that reduction in the number of new infections in China has been partially shadowed by the increase in the number of cases in other countries such as Italy, Spain, Korea, Japan, Iran, and the States, to the point that at present the number of deaths in Italy (7,503 as of March 26th, 2020) has surpassed those in China (3,288). A key question is how this epidemic will evolve next. World Health

Organization (WHO) experts such as Maria Van Kerkhove, who heads the WHO's emerging diseases and Zoonoses unit, and has recently visited China with an expert mission for two weeks, has concluded that, in fact "it seems that people shed more (virus) in the early phases rather than the late period of disease." That being the case, it will be much more difficult to break the chains of transmission and stop the virus.

Overall, data have shown that it is possible to control the epidemics in a densely populated country like China with high effort and discipline. Now a similar strategy is being followed in European countries. Fortunately, in the majority of the Chinese population affected by the Wuhan virus, the largest proportion of the patients (more than 98%) has elicited an immune response able to control virus progression and, in general, only those elderly adults infected by the Wuhan virus, with additional medical problems, deeply suffered from the Wuhan virus infection. Certainly, this important part of the population, soon could receive immune therapy by using serum collected from recovered patients. In addition, this therapeutic approach could soon be expanded with the application of novel monoclonal antibodies neutralizing SARS-CoV-2 that are under development. Although viruses developed their own strategies to invade human beings, the History of Medicine has shown that the battle between virus and host in general ends with the elimination of the virus.

About the authors



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