Evolution of SARS-CoV-2 in relation to the host immune system

"Nothing in Biology Makes Sense Except in the Light of Evolution"
Theodosius Dobzhansky (1900 – 1975)

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ABSTRACT

How can we explain the temporal evolution of the pandemic?

An analysis of the curves of the epidemic at the late stage shows the evolution towards the benignity of the virus throughout the world. There is a prolonged increase in new cases with a steady decrease in severe cases and deaths.

Cross-immunity with common cold coronaviruses has been suggested. This would involve viral sequences coding for the spike protein but also and importantly for non-structural proteins that could interact with the cellular immune response (CD4+ and CD8+).

The mutations in the viral RNA sequence observed during Covid-19 also concern regions involved in the interaction of the virus with cells of the host immune system. It appears that the emerging virus has adapted to the host immune system by altering its transmissibility and/or virulence. The virus adapts by natural selection to the immune system of its host (the human population); it is the sum of these individual adaptations that produces the overall evolution of the virus during the epidemic. This hypothesis is consistent with the Theory of Evolution, which often helps to solve puzzles in biology.

Introduction

Many questions regarding the progression of Covid-19 since the emergence of the SARS-CoV-2 virus remain unanswered.

Recent history should not be overlooked: the knowledge acquired during the SARS epidemic of 2003-2004 and the biology of common coronaviruses could suggest certain clinical, epidemiological and therapeutic aspects of SARS-CoV-2 (Freymuth et al., 2009, Groneberg et al., 2004): SARS-CoV had started its course in November 2003 and the epidemic was declared over at the end of June 2004 (with a few rare mild cases found until January 2004).

It seems that the explanatory hypotheses currently put forward do not refer to it enough: the role of cross-immunity with other coronaviruses (common cold viruses) was evoked in 2004 following the SARS-CoV-1 epidemic of 2003 (Gioia et al., 2004). In 2020 with SARS-CoV-2 , this phenomenon was also found.

Epidemiological data from Covid-19 in late spring 2020 may cast doubt on the stability of the virus with regard to its pathogenicity. As always in biology, the theory of evolution can enlighten us.

CROSS-IMMUNITY BETWEEN COVID AND OTHER CORONAVIRUS INFECTIONS

This is cellular immunity (for common coronaviruses, SARS and MERS, antibodies disappear after 2 to 3 years, cellular immunity persists for 11 years. (Ng et al., 2016).

Indeed, the role of humoral immunity has not been demonstrated in this cross-immunity. An April 2020 publication (Pinto et al. 2020) tests a monoclonal antibody isolated from a patient who survived SARS-Cov-1 from 2003 and attempts to show cross-neutralization of SARS-CoV-2 from 2019 . This monoclonal antibody is directed against the spike protein binding domain present on the surface of the virus and characteristic of coronaviruses. However, these are pseudoviruses (recombinant between MLV - murine leukemia virus and SARS); they are studying the neutralisation in vitro on Vero cells transfected with human ACE2 (thus a single "receptor" of the virus). So this study is too far away from what could happen *in vivo* and cannot prove humoral cross-immunity between SARS-CoV-1 and SARS-Cov-2.

So we have to look at cellular immunity to this virus.

Reminder on cellular immunity

CD4+ and CD8+ cells are effectors of cellular immunity and cooperate with the B-lymphocytes responsible for antibody production and thus humoral immunity. These cells are activated during an infection. These 2 cell types synthesize cytokines with different roles. CD8+ are rather "killer" lymphocytes capable of destroying infected cells by cytolysis and producing necrotizing cytokines, CD4+ rather produce interferons and interleukins which are cytokines effecting Th1 (oriented towards cellular immunity) and Th2 (oriented towards antibody production) responses. These cells are responsible for both beneficial (pathogen elimination) and deleterious (immunopathology) effects.

The role of cross-immunity with other coronaviruses (common cold viruses) was discussed in 2004 following the 2003 SARS-CoV-1 epidemic (Gioia et al., 2004).

In April 2020, in Berlin, Braun et al. investigated the cellular reactivity to SARS-CoV-2 in patients who had developed moderate to severe Covid-19. Only the epitopes (antigenic determinants) of the Spike protein were tested. Only CD4+ cells were tested (not CD8+).

83% of the patients had CD4+ cells reactive to the epitopes of the Spike protein. The cross-reactivity with common cold coronaviruses concerns spike epitopes different from the receptor binding domain. All healthy donors (not infected with Covid-19) had antibodies to HCoV (common human coronaviruses).

In April 2020 Grifoni (Grifoni et al ., 2020) studied the cellular response of young adults exposed to SARS-CoV-2 who had developed mild to moderate infection. The response of CD4+ and CD8+ cells is found in 100% and 70% of convalescents respectively. This reactivity is directed against all the epitopes tested (involving both structural and non-structural proteins) and is proportional to the presumed abundance of each protein in the infected cells. Thus the reactivity is not only directed against the Spike protein and its binding domain to the putative receptors of the virus in the target cells. CD8+ reactivity is not dominated by the spike protein. In most moderate Covid convalescents, the immune response was predominantly Th1 type with little or no Th2 response (the Th2 response is likely, like ADE (antibody dependent enhancement), to give immunopathological phenomena).

Grifoni et al. also sought and found this specific cellular reactivity to SARS-CoV-2 antigens in persons not exposed to Covid-19; this phenomenon could be quite widespread, as the reactivity of CD4+ cells is more widespread than that of CD8+ cells.

How can this cross-reactivity be explained? by the cellular response to common cold coronavirus (HCov). This reactivity is directed to the conserved parts of the structural and non-structural proteins of HCov and SARS-CoV-2. It is found in 40 to 60% of those not exposed to Covid-19.

Cross-immunity against common colds and SARS-CoV-2 is therefore highly probable.

In May 2020, a team from Singapore (Le Bert et al., 2020) searched for specific T cells that were associated with viral clearance in 24 convalescent patients with moderate to severe Covid.

This is the first study to examine memory as a function of the nucleocapsid protein rather than the Spike.

T-cells from people cured of 2003 SARS recognize the epitopes of the NP (nucleoprotein) of SARS-CoV-2. In people exposed to SARS-2, they have also recovered a cellular cross-reactivity with the HCov of common colds: it concerns the NP and also the NSP 7 and 13 of SARS-2 (contrary to SARS-1 exposures which do not have this reactivity, NSP = non-structural proteins).

And there is a cross-reactivity of CD4+ cells to NP in individuals who have encountered neither SARS nor Covid (also towards NSP7 and 13, unlike those exposed to SARS or Covid); these reactivities are found for epitopes common to SARS, Covid and cold coronaviruses.

Thus, there is indeed a cross-cellular reactivity towards SARS-Cov, common coronaviruses and

SARS-CoV-2. 50% of the unexposed (neither SARS1 nor SARS2) have cells specific for these NSP7/13 epitopes whereas the exposed rarely have them.

This confirms the work of Grifoni at al: the unexposed recognize non-structural proteins, the exposed recognize the NP nucleocapsid and structural proteins.

Hypothesis of the authors Le Bert et al :

The cellular response against structural proteins is induced by a productive infection of virions (SARS and Covid).

The cellular response would be limited to ORF1 epitopes of NSP7/13 in those exposed (but not infected) to the unknown coronaviruses.

This response to ORF1 may be necessary to abort virus production before the formation of mature virions. Indeed, ORF1 is necessary for the formation of viral replicase-transferase .

The ORF1 region contains domains that are highly conserved among many coronaviruses. The distribution of these viruses in different animal species could lead to periodic contact with humans and subsequent induction of ORF1-specific T cells with a cross-reactivity capability against SARS-CoV-2. T cells specific for viral structural proteins have a protective capacity in animal models of respiratory tract infection.

This study shows that there is cross-reactivity with NP and NSP epitopes (encoded by the ORF1 region) in individuals not exposed to SARS-CoV-2, thus suggesting cross-immunity between that directed against HCoVs from common colds and that against SARS-CoV-2.

These three studies are therefore in the same direction and tend to prove the existence of this cross-immunity between common colds and Covid-19. This immunity is logically directed against antigens common to all coronaviruses and not against SARS-Cov-2 specific antigens. These common antigens are found on the structural proteins N, M and Spike and also on non-structural proteins (including viral RNA replication enzymes). The non-structural proteins of the replication complex are encoded by the ORF1 region (which represents two-thirds of the virus genome). This cross-immunity could therefore explain the low percentage of Covid-19 patients in the population (except in the elderly and chronically ill).

It is not surprising to find this cross-immunity based on what is known about the distribution of common coronavirus infections.

The cellular immune response to common colds is inversely proportional to the duration of virus shedding, but independent of the severity of symptoms and antibody levels after recovery (Kirkpatrick, 1996).

HCov causes 15% to 20% of colds in adults (Greenberg, 2016).

HCov is found in 5.4% of adults hospitalized for low-level respiratory infection and in 3-8% of children under 5 years of age hospitalized with acute respiratory illness (Zimmerman, 2020).

In 2006 in Hong Kong, there were 200 hospitalizations per year per 100,000 children under 5 years of age due to HCoV. Children, the elderly and the debilitated are most likely to be hospitalized for respiratory symptoms due to HCov. (Van Der Hoek, 2006)

According to an epidemiological study (Gaunt, 2010); most individuals seroconvert to the 4 common HCOv known in childhood and these 4 viruses are detected in all age groups and with equal frequency, they cause infections throughout life.

EVOLUTION OF THE VIRUS

If we limit ourselves to the history of the epidemic on French soil, recent evidence shows that the virus arrived in October-November 2019. The first officially recorded cases in France (Stoecklin et al., January 2020,) date from mid-January, in Germany from the end of January (Rothe, March 2020), however a doctor from Alsace thinks that he saw dubious cases (a posteriori) in November 2019 (Schmitt, May 2020) with a very slow progression and an outbreak from the end of February. During the Military Games in Wuhan in mid-October, 2019 European athletes may have been infected and developed curious flu syndromes (RTL, May 2020, France TV, May 2020, Gouv.fr, October 2019).

In addition, a recent Harvard study (Nsoesie et al., 2020), shows a significant increase in hospital traffic and internet searches for symptoms associated with Covid from late summer 2019 in the Wuhan area. In particular, the gastrointestinal symptoms associated with Covid could explain why the beginning of the epidemic escaped the respiratory infection surveillance system. Moreover, it has been shown that children could transmit the virus by faecal route and not by respiratory excretion (Yi Xu et al., March 2020).

The molecular clock that gives an estimate of the date of emergence of the virus indicates an emergence between August and December 2019 (Van Dorp et al., Sept. 2020) but this mutational clock is not so accurate. For example, the speed of the clock (mutations/unit of time) may vary as the epidemic spreads. And the clock is calibrated based on the mutation rate of the available virus strains, not the initial strains. (Pierre Sonigo, 2020)

It is therefore possible that the emergence of the virus dates back to late summer 2019 in China and that it has penetrated as early as October 2019 (or earlier?) in the West. Why did the visible peak only occur from December to February in China and from the beginning of March to the end of April in France? The Marseille IHU, South of France, which began mass testing at the end of January, observed the first positive cases at the end of February 2020. The same phenomenon could be found throughout the world since the genomic diversity of the SARS-CoV-2 world population, summarized in many countries, indicates that the disease spread worldwide probably from the beginning of the pandemic (Van Dorp et al., 2020).

The authorities and the majority of scientists agree on the effect of the drastic health measures that would have interrupted the circulation of the virus. This was also the case in 2003-2004. If the virus was present in Europe as early as October 2019, it is difficult to see how lockdown from mid-March onwards could have had an effect. Similarly, if the virus emerged in China as early as the summer of 2019, it is hard to see how the lockdown imposed at the end of January 2020 could have changed the course of the virus. Sanitary measures are of course defended by those who promoted them (Imperial College, Flaxman et al., March 2020, June 2020, Okell et al., March 2020) and always by mathematical modelling (Acemoglou et al., May 2020), the confrontation of the models with the reality of what happened seems to be problematic.

Moreover, numerous studies have been published showing that the strict lockdown of the entire population is not responsible for the decline of the epidemic: not to be confused with the isolation of the sick and the targeted protection of vulnerable people. These studies look at the effect of confinement from different angles, but they all point in the same direction. They are based, contrary to the models already mentioned, on analyses of data collected during the epidemic.
(Toussaint, 13 June 2020; Zelmat, 26 May 2020; Pech de Laclause et al ;
Andolfatto and Labbé, 5 June 2020 ; Aslangul, 5 June 2020 ; Andolfatto and Labbé, 22 June 2020 ;
Le Bourg et al; Gøtzsche; Wittkowski; Raude, April 2020; Nordmann, 2 May 2020; Meunier T.A.J. 2020; Crowe, 20 June 2020).

Explanations based on mathematical modelling of R0 and kappa (dispersion factor) seem

insufficient to explain the epidemic curve (Korsia-Meffre, June 2020).

An analysis of the curves of the late-stage epidemic shows the worldwide trend towards the benignity of the virus. There has been a sustained increase in new cases with a steady decline in severe cases and deaths. It is important to base oneself on the speed of the curves and not on the raw figures of cases or deaths (even in countries where reliable statistics are available, large discrepancies exist depending on the counting methods, for example in France on the weekly " Point épidémiologique hebdomadaire Santé Publique" of 18 June 2020, "11,016 death certificates were found to contain a mention of COVID-19 among the medical causes of death listed" and above "Between March 1 and June 16, 2020, 29,547 deaths of COVID-19 patients were reported to Santé publique France" (Santé Publique France, June 2020).

The evolution of the viral population in relation to the immune system of its host (the world population) could explain the "accelerations" and "decelerations" of the virus as evoked by Pierre Sonigo for the evolution of AIDS in a given individual ("Ni Dieu, ni gène", Ed Seuil, 2005).

It is accepted that the virus emerges as a result of recombinations that allow it to cross the famous "species barrier"; then deletions and mutations allow it to continually adapt to its host (Freymuth et al;, 2009).

A small vocabulary is necessary: the word virus refers to the viral population which gathers all virions (virus individuals).

Each time a new human individual is infected, a more or less important quantity of virions is produced according to the immediate innate immune response. This population of virions adapts by natural selection to the immune system of its host (in particular to the "receptors" of the virus); it is the sum of these individual adaptations that produces the overall evolution of the virus during the epidemic. The term "immunity" refers both to a process and an outcome; there is an evolutionary race between the viral population and immunity as a process produced by the human population. This assumption is consistent with the Theory of Evolution, which often solves puzzles in biology. It is consistent with JJ Kupiec's theses on the apparent order at the macroscopic scale that results from disorder at the molecular level. ("Et si le vivant était anarchique?", Ed. Les liens qui libèrent, 2019)

The virus is transmitted at the beginning of the disease, i.e. before the host has been eliminated. It is a stochastic interaction at the level of billions of virions in front of billions of immune cells of the host each time a human is infected.

Virons that present antigens recognized with high affinity by the host cells (cross-immunity with other coronaviruses) are counter-selected. Indeed, they are destroyed faster than others by these cells. Only virions that do not react (or less) with these cells will be able to multiply and will therefore be selected. So each time a human is infected, the virions he will transmit will have mutated compared to those who infected him. Thus at the macroscopic level, mutations will appear in the global viral population which will go in the direction of an adaptation to the global immune system of the host. These mutations are homoplasia: they have appeared independently and are the result of an evolutionary convergence.

Immunopathological phenomena seem to be responsible for the severity of the disease (for SARS1 :Cameron, 2007 and for SARS-2 Vabret, 2020, King, 2020. Grifoni et al, 2020). Virions that stimulate these phenomena less, by interacting less with immune cells, would be selected and the virus would evolve towards a benign phenotype.

The following observations may support this hypothesis

Already in April 2020, modelling based on the evolution of the viral population in relation to the host immune system had been attempted. (Dimaschko and Podolsky, April 2020). This study models the epidemic in different countries, taking into account the evolution of the viral population towards less transmissibility and less virulence; the models are compared with actual curves in the world, in Russia, USA, South Korea, Germany, Spain, Italy. The comparison confirms that the epidemic develops according to the evolution of the virus and not to the group immunity acquired by the human population. The natural evolution of the viral population in contact with its host reflects the observed curves.

The study of the evolution of the SARS-CoV sequence in 2003-2004 had already suggested that mutations that appeared during the epidemic could explain its history (Drösten, 2018) (mutation in the ORF8 region). Already in 2003 the first SARS had evolved rapidly at the ORF8 level, with a deletion causing less active replication and attenuation of virulence. "ORF8 is one of the most relevant genes in the study of potential viral adaptation to humans. A deletion of 29 nucleotides within ORF8 has occurred in all strains involved in the mid- and late-phase human epidemic. Proteins encoded by the ORF8 of SARS facilitate viral replication regardless of the host cell system. Reduced initial fitness is a condition that can be expected in early stage zoonotic epidemics, when the virus is not yet adapted to the new host environment."

In 2020, for SARS-CoV-2, several studies confirm this tendency of the virus to evolve towards less virulence.

As early as April 2020 Van Dorp (Van Dorp et al.), show that mutations accumulated independently (by evolutionary convergence) during the temporal evolution of the epidemic, they concerned the ORF1 region (which codes for NSP6, a non-structural protein) and which contains homoplasia (mutations that appear independently) important for adaptation to humans. This region covers a peptide presumed to react with CD4+ and CD8+ cells of adaptive cellular immunity. Although the immune response to SARS-CoV-2 is still poorly understood, the key roles of CD4 T cells, which activate B cells to produce antibodies, and cytotoxic CD8 T cells, which kill virus-infected cells, are known to be important in mediating clearance in respiratory viral infections. Like most (but not all) pathogens capable of causing a pandemic-scale outbreak, SARS-CoV-2 is likely to be of zoonotic origin. This means that SARS-CoV-2 may not be adapted to its new human host, which would explain the accumulation of mutations in the area responsible for this adaptation.

Also in April 2020, a team in Arizona (Holland et al., May 2020) also found a deletion in the ORF7 region from the sequences deciphered at the beginning of the outbreak in Wuhan. This deletion was recovered from a pool of 382 sequences collected in late phase in Arizona. It concerns 81 nucleotides and 27 corresponding amino-acids in a region that could be important for the adaptation of the virus to humans (because it is close to the ORF8 region identified in 2003).

Again in April 2020, a team from Singapore found a deletion in the late phase of the epidemic in the ORF8 region (this deletion was found at the end of February 2020 in Singapore, which corresponds to the late phase for Asia) (Su et al., March 2020). The authors also suggest that the major deletion revealed in this study could lead to an attenuated SARS-CoV-2 phenotype.

In June 2020, an Italian publication was announced by Prof. Massimo Clementi from Milan (Il Giornale, June 2020), who also reportedly found mutations potentially responsible for the attenuation of the virus during the epidemic in Italy.

The mutations in the viral RNA sequence observed in these recent studies therefore concern regions involved in the interaction of the virus with cells of the host immune system. It thus seems to be confirmed that the emerging virus has adapted to the host immune system by modifying its

transmissibility and virulence. This adaptation is thought to have occurred in fits and starts in the Wuhan region, after a phase of relative latency characterized by an epidemic of ill-defined syndromes in the summer of 2019 until the SARS outbreak in December. Similarly, when it arrived in the West in autumn 2019, the virus would have made its way through a genetically different population and would have finally flared up in March 2020 after having acquired mutations favouring its transmissibility and respiratory virulence. All this can only remain speculative since the mutations between the time of its supposed emergence and the start of the outbreak can never be studied, due to the lack of genomic sequences collected during the "latency" period.

This is also observed for the influenza virus which is adapted to humans and is not an emerging virus. During the winter of 2018-2019, in Canada, antigenic drift from the H1N1 subtype to the H3N2 subtype was observed between January and March 2019. This drift allows the virus to reach different populations depending on their age; in fact, it has been demonstrated that there is an antigenic imprinting phenomenon for influenza: individuals are more or less sensitive to one subtype or another depending on their age and on the subtype encountered for the first time in their lives (Gagnon et al.). Here again, this can be interpreted as an evolution of the virus in relation to the host immune system, the virus returning this time to a subtype that has already appeared previously, contrary to the case of SARS-CoV-2, an emerging virus.

CONCLUSION

It is not impossible that all common cold coronaviruses, when they jumped from animals to humans (they are all originally responsible for zoonoses), began their evolutionary course like SARS-CoV-2 with a pandemic like Covid-19.
But at the time, the means of investigation in virology and molecular biology did not exist and were not identified.

Other cold coronaviruses are known to be common viruses; it is not impossible that SARS-Cov-2 could become a common coronavirus after mutations.

As explained by Prof. Didier Sicard (Sicard, June 2020), further pandemics of this type are to be expected due to the abundance of zoonotic viruses circulating in close proximity to humans as a result of Asian dietary habits and the profound changes in the ecology of the planet produced by human activity.

Preparation for this would require, at a minimum, effective monitoring of the circulation of respiratory viruses in all countries. In France, is the current surveillance system for influenza syndromes in ambulatory medicine "Sentinelles" and "GrippeNet" sufficient to face such challenges? One can doubt it when one reads that between June 1st and June 7th, 2020, this network has analyzed only 128 suspicious samples of Covid for the whole country (Point épidémiologique hebdomadaire Santé Publique France, June 11th, 2020), and 152 samples at the beginning of March, thus well before the deployment of specific tests for Covid but already in full outbreak (Bulletin hebdomadaire grippe Santé Publique France, March 11th, 2020).

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