Covid19: cross-immunity with other coronaviruses, immunopathological phenomena

August 2020 update

SUMMARY

The low percentage of individuals in the population with symptomatic Covid-19 can be explained by cross-immunity with other coronaviruses. This phenomenon is based on cellular immunity. On the other hand, humoral immunity (antibody-mediated) could be partly responsible for some immunopathological phenomena.

The balance between this beneficial cellular immunity and these immunopathological phenomena could explain on the one hand the low representation of children among the sick and on the other hand the high lethality in the elderly.

In order to face a future pandemic, it would therefore be necessary to find out how to protect fragile populations on the one hand and improve the immune status of the world's population from a global health point of view on the other hand.

This is not only a health problem but a social problem and also an economic problem such as the state of the health system of the planet.

INTRODUCTION

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

Recent history (with the knowledge gained from the SARS epidemic of 2003-2004 and the biology of common coronaviruses) should not be overlooked (Freymuth et al., 2009, Groneberg et al., 2004). It seems that the explanatory hypotheses currently put forward do not refer to them sufficiently.

The role of cross-immunity with other coronaviruses (common cold viruses and SARS-CoV-1) has been suggested to explain the low proportion of people who have developed Covid-19 (and apparently the low proportion of people who are HIV-positive with the currently available tests).

CROSS-IMMUNITY BETWEEN COVID AND OTHER CORONAVIRUS INFECTIONS

This is cellular immunity (for common coronaviruses, SARS and MERS, antibodies disappear after 2-3 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 the 2003 SARS-CoV-1 and attempts to show cross-neutralization of the 2019 SARS-CoV-2 . This monoclonal antibody is directed against the spike protein binding domain present on the surface of the virus and characteristic of coronaviruses. But they are pseudoviruses (recombinant between MLV - murine leukemia virus and SARS); they study the neutralization in vitro on Vero cells transfected with human ACE2 (thus a single "receptor" of the virus). Thus this study too far from what could happen in vivo cannot prove a humoral cross immunity between SARS-CoV-1 and SARS-CoV-2. Furthermore, the results of Sekine et al (June 29, 2020) and Gallais et al (2020) confirm that antibodies play little role in acquired immunity against SARS-CoV-2 compared to cellular immunity.

The focus should therefore be on cellular immunity against this virus.

Serology (search for antibodies, therefore humoral immunity) will be discussed below in relation to

the immunopathological phenomena found in Covid-19.

Reminder on cellular immunity

CD4+ and CD8+ cells are effectors of cellular immunity and cooperate with B lymphocytes responsible for the production of antibodies 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 effector cytokines of 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 SARS-CoV-1 epidemic of 2003. (GIOIA, 2004) What about SARS-CoV-2 in 2020?

In April 2020, Drosten's team in Berlin (Braun et al., 2020) investigated the cellular reactivity to SARS-CoV-2 in patients with moderate to severe Covid-19. Only 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) .

Also in April 2020 Grifoni et al. are studying the cellular response of young adults exposed to CoV-2-CASR and who have developed mild to moderate infection.
The epitopes tested are all those of the Spike as well as M (membrane) ,N (nucleocapsid) structural proteins and NSP non-structural proteins: 100% of CD4+ and 70% of CD8+ of cured patients are reactive. CD8+ reactivity is not primarily directed against spike epitopes.
A reactivity of cells of the unexposed is found towards antigens of the conserved parts of the structural and non-structural proteins of the HCoV: cross-immunity against common colds and SARS-CoV-2 is therefore highly probable.

The same team (Mateus et aL., 2020), confirms their work and further shows that CD4+ cells showing cross-reactivity with homologous amino acid sequences of SARS-CoV-2 and HCoV are memory cells. The greater the homology, the stronger the cross-reactivity. Sekine et al. find the same results in Sweden (Sekine et al., 2020) concerning the presence of memory T cells in people with moderate or asymptomatic Covid.

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 team demonstrated a reactivity towards epitopes of the nucleocapsid and non-structural proteins of the ORF1 region. The ORF1 region contains domains that are highly conserved among many different coronaviruses. T cells specific for viral structural proteins have protective capacity in animal models of respiratory tract infection.
This study shows that there is cross-reactivity with NP and NSP epitopes in individuals not exposed to SARS-CoV-2, thus suggesting cross-immunity between that directed against HCoVs from common colds and that directed against SARS-CoV-2.

Finally Gallais et al . 2020, confirm this cross-reactivity with HCoV, particularly in pauci or asymptomatic patients who are seronegative to specific epitopes of SARS-CoV-2 and PCR negative. The serologies were performed with 3 different tests (one using the lateral flow technique) and the epitopes tested belonged to the nucleoprotein and the spike protein (surface protein) of

SARS-CoV-2.

Cellular immunity was tested by measuring the synthesis of gamma interferon by T cells stimulated by a pool of epitopes including the entire spike, NP epitopes and membrane proteins (M and E) of SARS-CoV-2.
Cross-reactivity with HCoV is tested with the spike of HCoV 229E and OC43.
The study compares exposed and symptomatic caregivers with their pauci or asymptomatic contacts. The index patients are HIV positive, the contacts are HIV negative.
The contacts belong to the index families. PCR is positive for all index patients and negative for all contacts. All indexes have a cellular response to SARS-CoV-2 (S1, S2, M and N at least). Six out of 8 contacts have a cellular response (mainly towards structural proteins and to a lesser extent towards the spike). Virtually all donors (healthy, index and contacts) have a response to the HCoV spike.

Therefore the cellular response is more sensitive than serology. An asymptomatic contact also develops a cellular response. Cellular responses to HCoV epitopes are equivalent in index, contact and healthy donors. Responses to specific epitopes of SARS-CoV-2 are not observed in healthy donors.

One explanation is proposed: exposure to low doses of virus could induce brief replication of the virus in mildly exposed individuals; innate immunity could abort extensive replication of the virus.

These studies are therefore along the same lines 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). 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.
Immunity to common cold viruses: the cellular response is inversely proportional to the duration of virus shedding, but independent of the severity of symptoms and the level of antibodies after recovery. Kirkpatrick, 1996

HCoVs causes 15% to 20% of colds in adults (Greenberg 2016)
HCoVs are found in 5.4% of adults hospitalized for low respiratory infection, in 3-8% of children under 5 years of age hospitalized with acute respiratory illness (Zimmerman, 2020).
In 2006 in Hong Kong, 200 hospitalizations per year and per 100,000 children under 5 years of age were due to HCoVs. Children, the elderly and the weak are most likely to be hospitalized for respiratory symptoms due to HCoVs. (Van Der Hoek, 2006)

According to an epidemiological study, most individuals seroconvert to the 4 common HCOv viruses known in childhood and these 4 viruses are detected in all age groups and at equal frequency, they cause infections throughout life. Seroprevalence against HCoVs increases rapidly during childhood and remains high in adults (Gaunt, 2010). There is no clear trend in the relationship of seroprevalence with age, and the incidence of coronavirus infections is high in the elderly (Huang et al., 2020).

ARE CHILDREN LESS AFFECTED?

There is increasing evidence that children are as affected as adults but only very rarely develop the disease and even more rarely a severe disease (see the epidemiological bulletins Santé Publique France, among others). In a publication in early June (IHU, 2020) the IHU Marseille

shows that the proportion of children testing positive is slightly lower than that of adults, the viral load of children is slightly lower than that of adults and the duration of virus excretion is shorter.

In Berlin in June 2020, Drosten and his team (Jones, 2020) found no significant difference between viral loads in children and adults. Children are reportedly as capable as adults of transmitting the virus and, as in Marseille, they are contaminated in homes since schools were closed.

(Note on "viral load": this term can mean two different things.
Either the quantity of virions that infects an individual during the contagion, or the quantity produced by this individual following the contagion and the multiplication of the virus in the target tissues. It is this viral load that is estimated by Rt-PCR.
The first quantity (viral load at the time of contagion) is simply assumed, to measure its impact it would be necessary to undertake voluntary contagions with different viral loads on humans, which is obviously not possible. But it is accepted in virology that this initial viral load greatly determines the evolution of the disease).

Concerning the very low representation of children among the sick, the role of cross-immunity with common colds has been advanced: this is debatable. Indeed, as seen above, all age groups of the population are regularly affected by common coronaviruses and present immunity to them. We will see below, in the discussion of the immunopathological phenomena that the reverse could also be the case given the increased cumulative number of HCoV infections in older patients.

Other hypotheses to explain children's resistance to the disease are listed by King, 2020. He discusses the role played by the "receptor" of the virus, ACE2, and its greater or lesser expression in children; it seems difficult to attribute such a phenomenon of resistance in children to the single variable of one of the identified receptors of the virus.

INNATE IMMUNITY, IMMUNOPATHOLOGICAL PHENOMENA, ROLE OF ANTIBODIES

Innate immunity, immunopathological phenomena

As early as 2007 (Cameron, 2007), the decisive role of innate immunity and immunopathological phenomena had been evoked with regard to SARS-CoV-1: this innate antiviral immunity is characterized by the production of interferons. The deficiency of innate immunity allows the virus to multiply (immune escape of the virus); following the high viral load to which the patient is then subjected, immunopathological phenomena develop.

Aging is associated with a decline in the competence of the immune system, called immunosenescence, affecting both the innate and adaptive compartments. It is associated with a second phenomenon called "inflamm-aging" characterized by an increased production of proinflammatory cytokines. All of these changes reduce the ability of the elderly patient to produce an effective immune response (Vallet et al., 2019).
According to Grifoni, 2020, in the elderly, APCs (antigen presenting cells) function less well and present the antigen to myeloid cells poorly, thus there is immune evasion of the virus and amplification of immunopathological phenomena because large quantities of virus are produced.
The presence of excessive inflammation prevents immunity. Healthy people over 60 years of age have a chronic inflammatory state (not caused by pathogens) with high levels of CRP and cytokines (IL-6, IL-8). This excessive inflammation inhibits immunity in vivo. Senescent cells secrete proinflammatory mediators, they are normally eliminated by T cells and NKs. These senescent cells may participate in the inflammatory cascades during an infection with SARS-CoV-2 (Akbar and Gilroy, 2020).
According to Vabret, 2020, King, 2020. Grifoni et al, 2020, severe forms of SARS-CoV-2 are associated with large amounts of cytokines, and these cytokines are associated with

immunopathological phenomena.

Immunocompromised patients (treated with immunosuppressive drugs following a recent transplant) have presented benign Covid: only those who had co-morbidities known to increase the risk of Covid had severe Covid. (Bhoori et al., 2020)

The SARS of 2003-2004 is closer to Covid-19 than the references made there today. Its clinical characteristics were finally quite comparable to Covid (and partly also to those of coronavirus diseases common in immunocompromised people): the severity of these infections is always determined by the patient's condition.

A 2008 publication concerning SARS from 2003 (Li, 2008) shows a shift in the balance of Th1 (protection-oriented) and Th2 (inflammatory phenomenon-oriented) immunity in the elderly in favor of the latter.

In 2020, immunologists are taking up this hypothesis: Kingston Mills of Trinity College Dublin and Stanley Perlman of the University of Iowa, also evoke this balance between Th1 and Th2 immunity that differs according to age (King, 2020).

Role of antibodies in these immunopathological phenomena

Numerous publications correlate the severity of Covid-19 disease with circulating antibody levels (Gorse et al., Bo Hansen C et al;, 2020, Yu, 2020, Grzelak, April 2020). The more severe the disease, the higher the antibody levels.

Similarly the results of Xin Xu (Xin Xu et al., 2020) suggest that only severe Covid patients make antibodies against the Spike surface protein.

Common Elisa tests are very specific for this protein, hence the very low seroprevalences found here (3.5% on average in Wuhan).

People infected but with few or no symptoms do not develop this type of antibodies specific to SARS-Cov-2, they would have been protected by their cross-immunity to common cold coronaviruses. We have seen above that this cross-immunity was directed against antigenic determinants that are not specific for SARS-CoV-2.

In Zürich (Cervia et al., 2020) patients with moderate Covid had low levels of Spike-specific serum IgG and IgA. Patients with severe Covid have higher IgG and IgA levels the more severe the disease.

Orthodox immunological theory will tell us that antibodies are synthesized in larger amounts to defend the patient against the virus.

On the contrary, it can be said that the high level of antibodies is partly responsible for the severity of the disease: the immune dysfunction due to the patient's inadequate response to the infection induced a Th2 (humoral and inflammatory) rather than a Th1 (cellular) type reaction.

What is the cause of this inadequate response?

Certainly the overall poor health status of patients with severe Covid (almost all of them had co-morbidities).

How can the high antibody level explain the worsening of the disease?

In part, certainly at least, by the facilitating effect of the infection caused by the antibodies.

(as proposed for SARS1: Cameron, 2007). For a comprehensive review of the antibody-facilitating effects of antibodies in many viral infections, see Taylor et al. 2015; for coronaviruses: Wan et al. 2020; Roper and Rehm 2009.

A molecular biology publication could confirm this mechanism (Wan et al., 2020).

It shows masterfully (but far from what can occur in vivo when a human is infected with SARS-CoV-2), that the phenomenon of ADE (antibody dependent enhancement, facilitation of antibody-mediated infection) could explain the second phase of degradation of the clinical state in some patients.

This study was published in March 2020, it concerns SARS-CoV 2003 and MERS but given the proximity of SARS-CoV-2 to SARS-CoV, it could be valid for SARS-CoV-2.

It is demonstrated in vitro that these first 2 viruses have cell penetration facilitated by antibodies binding to the spike protein (at the receptor site). Coronaviruses have been known for decades to present this ADE, like other viruses (dengue, ebola, HIV, etc...), but what is shown here, unlike other viruses, is that ADE can occur with the same strain. Conversely, all the ADEs shown so far have been shown with strains that are close but antigenically different.
The ADE here would depend on the level of antibodies, the tissue specific expression of viral and Fc receptor receptors of immunoglobulins and the intrinsic characteristics (affinity) of the antibodies produced.

In vivo, this mechanism could explain the rebound of the disease.

In weakened patients, innate immunity would be unable to eliminate the virus and then, when antibodies appear, they would cause ADE by invading tissues with specific receptors. These antibodies could also be concomitant with the Th2 immune response, which is characterized by an exaggerated inflammatory response. Indeed, antibody levels are higher in severe patients (Okba et al., 2020 and references cited above) and receptor-binding and neutralizing antibodies are higher in older adults (Gorse et al., 2020).

In healthy people, innate immunity is capable of strongly limiting viral multiplication and avoids the second stage of the disease (the inflammatory stage). This innate immunity is mediated by cells that are non-specific for a particular antigen; the innate response is rapid and capable of eliminating the virus before the adaptive antibody-producing response occurs (Fafi-Kremer, 2020).

There is a wide repertoire of antibodies that neutralize and/or bind in vitro to SARS-CoV-2 epitopes: some of these antibodies are specific for SARS2 (Premukar et al., 2020, and Yuan et al., 2020) and others exhibit high cross-reactivity with HcoV (Wec et al., 2020). The presence of these cross-reactive antibodies could raise concerns that they may facilitate SARS2 infection by previous HCoV infections.

Severe Covid cannot be linked to an ADE caused by antibodies produced during previous infections with other coronaviruses (HcCoV or SARS1 or MERS) as suspected by Kadkhoda.

This hypothesis is not supported by Mateus et al.: only T cells reacting to epitopes common to SARS2 and HCoV are specifically activated in Covid, unlike T cells reacting to epitopes specific to HCoV which are not.

The work of Sekine and Gallais shows that exposed but pauci or asymptomatic individuals show a robust cellular response to SARS2 while being seronegative for SARS2-specific antibodies. This is also a strong presumption that no ADE can be suspected: these individuals all possess antibodies against HCoV, so these cross-reactive antibodies are unable to induce an ADE to SARS2. Only antibodies specific to SARS-CoV-2 would be capable of doing so. This confirms the fears expressed by many experts regarding possible ADE with future vaccines. (Launay O, Floret D, 2020, Hotez, 2020 , Peeples L., 2020 ; Iwasaki A & Yexin Y., 2020)

CONCLUSION

One could conclude from all this that research on the structure of the virus and the specific immunity developed by its host is necessary but cannot be sufficient to anticipate a future pandemic with an emerging virus. As a result of this knowledge of CoV-1-CoV-SARS and the rapid sequencing of the emerging virus, it was known early on that the virus responsible for Covid was a close cousin of the 2003 SARS.

At the public health level, overall population immunity and the state of the health care system are the most important variables.

Severe cases of Covid have appeared in individuals with a weakened immune system (elderly, immunocompromised, diabetics, obese, etc.). To face a future pandemic, it would therefore be necessary to seek how to protect fragile populations on the one hand and improve the immune status (specific non-innate immunity) of the world's population from a global health point of view on the other hand.
This is not only a health problem but a social problem and also an economic problem such as the state of the health system of the planet.

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