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Editorial

Are previous viral infections important for the COVID-19 outcomes?

Since the beginning of the COVID-19 pandemic in early 2020, most of the research worldwide has focused in understanding the pathogenesis of this disease, yet the description of the role of coinfections between SARS-CoV-2 and other viral agents, and their association with the clinical manifestations of COVID-19 is still limited. Moreover, the potential impact that previous viral infections could have on the development of COVID-19 is still to be understood. Considering the clear association between metabolic-related diseases and the severity of COVID-19, as well as the rapid deterioration of patients due to SARS-CoV-2 induced immunopathogenic events, the impact of other viral infections known to alter the physiology of the host at both, metabolic and immune levels should be considered to gain a better understanding of the progression of COVID-19 in certain populations.

Recent metabolomic studies have demonstrated that some members of the *Flaviviriade* family, such as Hepatitis C virus (HCV) and dengue virus (DENV) cause profound metabolic alterations that can persist upon viral clearance. Interestingly, both flaviviruses affect liver function, and as well as other hepatotropic viruses such as Hepatitis A virus (HAV), have been associated with changes in the adaptive immune responses and it might have influence on development of subsequent viral diseases.

Several host factors related to liver metabolism such as lipids and lipoproteins promote the attachment and entry of HCV into their target cells and promote viral replication. Indeed, the lipid metabolism favoring triglyceride accumulation in the liver has long been recognized as an exceptional feature in the liver biopsies of HCV infected patients [1] and evidence for a high prevalence of metabolic alterations such as hepatic steatosis, insulin resistance, dyslipidemia, obesity, and diabetes mellitus related to HCV infection have also been identified [2]. Furthermore, endocrine-metabolic alterations are frequently found in chronically infected HCV patients and seem to be caused by the alteration of hosts glucose metabolism and changes in adipocytokines released from the adipose tissue. Notably, how all these alterations resulting from HCV infection might affect a secondary infection with a different viral agent is not fully clarified.

The effective use of vaccines and antibiotics combined with massive programs of sanitization resulted in a shift in the human disease spectrum, reducing the incidence of infections and increasing the incidence inf allergies during the 1980s. The hygiene hypothesis emerged as an attempt to explain this phenomenon, attributing it to the potential effect of an immune system not adequately trained to fight infections. This hypothesis is supported by studies revealing an inverse association between allergies and endemic infections caused by viral pathogens, such as HAV which is mostly transmitted by the fecal–oral route and agrees with David Strachan's proposal arguing that allergies might be prevented by viral infections transmitted by "unhygienic contact" during early childhood [3]. In fact, a protection against atopy, allergic sensitization and decreases in IgE levels mediated by HAV infections, mostly acquired during childhood, has been reported. These findings are consistent with the pattern observed in most developing countries where HAV infection remains widespread, and allergies are less frequent than in western countries, where the incidence of HAV infections is lower and where the incidence of allergic diseases has increased. Furthermore, recent findings support the idea that the solely existence of an anti-HAV immune response is not enough to protect against the manifestation of allergic diseases, as is the intensity and quality of this response. Indeed, an inflammatory cytokine-related profile during HAV infections contributes with the severity of disease and may be associated to the development of distinct clinical outcomes, including a more effective protection against allergies [4]. However, how HAV infection may affect the immune response underlying posterior infections has not been determined.

It has been well documented that in the scenario of different infections occurring closely together in a short timeframe, the innate immune response to one or both pathogens can affect the outcome of either diseases. More strikingly, it has been described that when infections are separated in time, the adaptive immune response to the first infection also plays a critical role on the clinical manifestations of the second one. In addition, some viral infections are highly suppressive to the immune system and may disrupt the immune responses against posterior infections. Measles Virus (MV) is one of the most immunosuppressive pathogens known to date, and individuals with clinical measles usually suffer from immunopathogenic events during secondary infections. A recent striking study underscored that, after recovery of MV infection, host immunity function is restored, but humoral immune memory is eliminated altering previously acquired memory [5]. This "immunological amnesia" gives vulnerability to subsequent infections and undoubtedly represents a challenge during the emergence of new viral pathogens.

Another situation which resets the immune response, affecting the mechanisms responsible for protective immunity, corresponds to the viral strategies that interfere with effective host immunity in a process known as immune evasion [6]. The immune evasion processes may also alter the response to heterologous infections (secondary infection) by causing changes on the adaptive immune response elicited towards the first infectious agent. An example involves the secondary infections caused by heterologous DENV serotypes, that in some infected patients are associated to the development of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), resulting from a severe inflammatory reaction. This exacerbated inflammatory reaction has been mainly associated to an immune process called antibody dependent enhancement (ADE) characterized by the production of sub-neutralizing antibodies that facilitate viral entry to inflammatory cells, and with the production

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of low avidity CD8 T cells which act as mediators of immunopathological events rather than controlling the infection [7]. These events, usually triggered by secondary DENV infections with heterologous serotypes, have not been analyzed during secondary infections with viruses different to DENV. Recently, powerful metabolomic techniques have been consistently used to identify changes in the levels of aminoacids, dicarbocylic acids, fatty acids and other tricarboxylic acid cycle-related metabolites induced by DENV infection [8,9], yet the role of these metabolic signatures and the way in which they might alter subsequent viral infections and thus, disease outcome has yet to be analyzed.

Despite the progress of virology, vaccinology, and the development of antivirals in recent years, we still have many successful viral infections that pose a risk for susceptible individuals. Moreover, in recent years we have faced the continuous re-emergence and emergence of viral pathogens such as highly pathogenic avian influenza viruses (HPAI), Ebola virus (EBOV), Chikungunya virus (CHIKV), Zika virus (ZIKV) [10], and more recently SARS-CoV-2, demonstrating the importance of viral infections for the public health systems worldwide.

We still do not know the impact that infections caused by DENV, HAV and HCV can have on the development of COVID-19 caused by SARS-CoV2. Liver function is altered because of infection with all these viruses. Therefore, it is important to continue studying the relationship of these etiologies in endemic regions to DENV, HAV and HCV; especially considering that these viral agents are mainly distributed in vulnerable and marginalized populations.

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