Review
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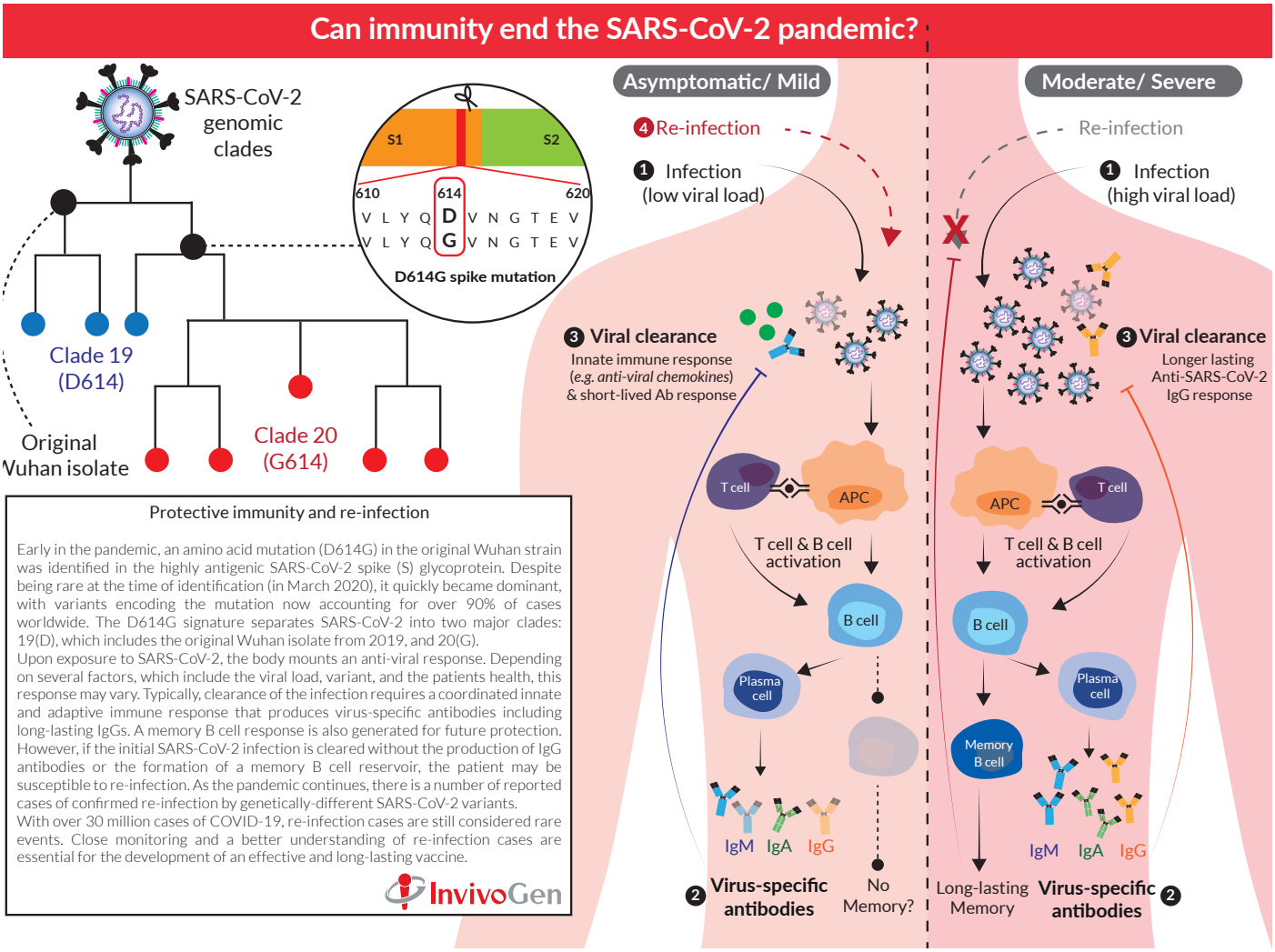
Spotlight on COVID-19
Protective immunity & Re-infection

Re-infection and what it means for long-term immunity and vaccine development

As our understanding of COVID-19 continuously progresses, some essential questions remain open including "Does protective immunity develop after SARS-CoV-2 infection?" and "How long does it last?" There is growing evidence that re-infection by SARS-CoV-2 can occur, indicating that immunity is either not strong enough, or not long-lasting in all individuals [1]. Therefore, it is crucial to elucidate the conditions entailing re-infection, to better apprehend the development of an effective vaccine against SARS-Cov-2. [1].



Protective immunity and re-infection

Early in the pandemic, an amino acid mutation (D614G) in the original Wuhan strain was identified in the highly antigenic SARS-CoV-2 spike (S) glycoprotein. Despite being rare at the time of identification (in March 2020), it quickly became dominant, with variants encoding the mutation now accounting for over 90% of cases worldwide. The D614G signature separates SARS-CoV-2 into two major clades: 19(D), which includes the original Wuhan isolate from 2019, and 20(G).

Upon exposure to SARS-CoV-2, the body mounts an anti-viral response. Depending on several factors, which include the viral load, variant, and the patients health, this response may vary. Typically, clearance of the infection requires a coordinated innate and adaptive immune response that produces virus-specific antibodies including long-lasting IgGs. A memory B cell response is also generated for future protection. However, if the initial SARS-CoV-2 infection is cleared without the production of IgG antibodies or the formation of a memory B cell reservoir, the patient may be susceptible to re-infection. As the pandemic continues, there is a number of reported cases of confirmed re-infection by genetically-different SARS-CoV-2 variants.

With over 30 million cases of COVID-19, re-infection cases are still considered rare events. Close monitoring and a better understanding of re-infection cases are essential for the development of an effective and long-lasting vaccine.

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THE OCCURRENCE OF RE-INFECTION

The first case of 'true' re-infection was published in August 2020 and with over 30 million cases of COVID-19 worldwide, they are considered a rare event. To date, there have been fewer than 30 reports (/covid-19-reinfection-tracker/). However, much more information is needed to understand if re-infection may be a more common event than currently appreciated. Thus, it is critical to differentiate cases that are SARS-CoV-2 positive over longer periods of time, due to prolonged viral shedding, from cases of true re-infection. Global health agencies, such as the CDC, have begun to establish a set of guidelines to ensure the identification of re-infection cases. Specifically, CDC states that 'a gold-standard confirmation of SARS-CoV-2 re-infection will require confirmation of initial infection and virus detection across two distinct time periods with genetic sequencing data needed to support a conclusion of high probability that re-infection has occurred' [2]. Therefore, in a suspected re-infection case, it is particularly important to establish that the two infections were caused by different variants of SARS-CoV-2.

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SARS-COV-2 VARIANTS

As of November 2020, the extraordinary sequencing efforts have produced over 170,000 SARS-CoV-2 genomes with the understanding of evolutionary trends paramount in controlling the pandemic [3]. SARS-CoV-2 sequences have been divided into a number of different clades that are characterized by specific genetic signatures. One of the most defining signatures is the first reported mutation to the SARS-CoV-2 Spike (S) protein, D614G. This mutation is thought to facilitate the infectivity of the virus, possibly by increasing the binding affinity between the spike protein and the host cell receptor, ACE2 [4,5]. Early in the pandemic, variants encoding the D614G mutation quickly became dominant around the world, and now they account for over 90% of infections (GISAID,2020). The D614G signature separates SARS-CoV-2 into two major clades: 19(D), which includes the original Wuhan isolate from 2019, and 20(G), which encompasses the expanding number of variants that derive from the G614-variant. Furthermore, additional mutations in the Spike, Nucleocapsid (R203K and G204R), and non-structural proteins, such as ORF1ab and NSP3, characterize various subclades [3]. The implications of these mutations remain elusive, with studies needed to decipher their impact on virus fitness and the host immune response. Recently, a report has described two novel European subclades that stem from clade 20(G), defined by two additional mutations in the Spike protein, A222V and S477N [6]. It is important to remember that despite many mutations being reported for SARS-CoV-2, the vast majority of them are inconsequential and do not affect the virulence and/or infectivity of the virus.

DISEASE SEVERITY AND RE-INFECTION

Re-infection is well-documented for the known 'common-cold'-causing coronaviruses, e.g. hCoV-OC43 and hCoV-HKU1, with an estimated period of 45 weeks of protective immunity [7]. It is likely that the reported cases of SARS-CoV-2 re-infection are largely under-estimated due to a lack of comprehensive testing, particularly early in the pandemic. But an important question that arises is "Who is susceptible to SARS-CoV-2 re-infection?"

To date, confirmed re-infection cases (reported in published or preprint articles) have been identified in Hong Kong [8], Brazil [9], Belgium [10-11], Netherlands [12], US [13-15], India [16-17], Qatar [18], Ecuador [19], and South Korea [20]. Interestingly, there are both commonalities and differences between the cases, with the majority in relatively young immunocompetent individuals. The change in severity between the initial and secondary infection is not homogenous, with cases of both milder and more severe symptoms upon re-infection. Variables such as the virus load, changes in the person's overall health, occurrence of antibody-dependent enhancement (ADE) [21], and differences between variants of SARS-CoV-2 could all affect the severity of a re-infection. Many of the reported cases of re-infection highlight that there is a significant number of genomic differences between the viral strains causing the initial and secondary infection. Interestingly, upon the classification of the viral strains, the majority of re-infection cases show that the variants are part of different clades. For example, in a reported re-infection from Ecuador, it was established that the patient was originally infected with a G614-variant from clade 20, however, the second infection was due to a variant from clade 19, a descendent of the original Wuhan isolate (D614-spike) [19].

Recovery from COVID-19 is associated with the production of anti-SARS-CoV-2 antibodies, but it remains uncertain whether they confer long-term immunity [14, 22]. In a number of the re-infection cases, antibody testing was not performed after the initial infection. Those with data suggest that, after the initial infection, the individual did not mount a sufficient neutralizing IgG response, which was only developed after their second infection [8, 19]. Typically, the immediate host response to SARS-CoV-2 infection is governed by the innate immune system, which is then followed by an early antibody response. The production of high titers of virus-specific IgM, IgA, and IgG antibodies peaks 3-4 weeks after the onset of symptoms, then declines. IgM and IgA levels were found in some patients to reach baseline levels 2 months after onset, while IgG levels remained high in most patients up to 3 months. Interestingly, the magnitude and longevity of the antibody response to COVID-19 appears to be associated with disease severity. Short-lived immunity has been especially noted in patients that experienced an asymptomatic infection or mild illness [22]. This suggests that they only developed a low neutralizing antibody response, with the virus effectively cleared by the innate and early antibody response. Thus, these patients may be susceptible to re-infection. In the more severe cases of COVID-19, high titers of neutralizing antibodies were detected, and importantly, no re-infection cases of immuno-competent individuals have been reported thus far.

CONCLUSION

Most people mount an effective immune response against SARS-CoV-2 with re-infection cases still considered rare. However, reports have suggested that the viral-clearing antibody response of asymptomatic/mild cases of COVID-19 wanes rather rapidly (< 90 days). Consequently, these individuals may be susceptible to re-infection. Therefore, there remains a tremendous need to develop our understanding of the host immune response against SARS-CoV-2 for the development of an effective and long-lasting vaccine strategy.

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