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Short communication

SAR-CoV-2 infection, emerging new variants and the role of activation induced cytidine deaminase (AID) in lasting immunity

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ABSTRACT

As the world faces a fourth COVID-19 spike, scientists are learning a lot more about the new SARS-CoV-2 strains that were previously unknown. Currently, the Delta versions of SARS-CoV-2 have become the prevalent strains in much of the world since it first appeared in India in late 2020. Researchers believe they have discovered why Delta has been so successful: those infected with it create significantly more virus than those infected with the original strain of SARS-CoV-2, making it extremely contagious. This has redirected the focus to how our immune system defends us from these various pathogens and initiates such varied responses. Hundreds of research papers have been published on the origins of long-lasting immune responses and disparities in the numbers of different immune cell types in COVID 19 survivors, but the primary architect of these discrepancies has yet to be discovered. In this essay, we will concentrate on the primary architect protein, activation induced cytidine deaminase (AID), which triggers molecular processes that allow our immune system to produce powerful antibodies and SARS-CoV-2 specific B cells, allowing us to outwit the virus. We believe that if we ever achieve permanent immunity to SARS-CoV-2 infection, AID will be the key to releasing it.

1. Introduction

SARS-CoV-2 first appeared on the global scene in December 2019. Until mid-2020, It wreaked havoc on humanity across the world. The scientific community hastened to exterminate the virus through investigations and research that culminating into what is called a V-Day when on December 8, 2020, Ms. Margaret Keenan became the first person to get the Pfizer Covid-19 shot as part of a mass immunization program (https://www.nature.com/articles/d42473-020-00431-2). Even though people had suffered immensely because of the SARS-CoV-2 outbreaks, they across the world took a sigh of relief due to the development of various types of vaccines against the virus. Following vaccination, researchers predicted that communities would develop herd immunity to SARS-CoV-2, lowering the risk of infection even among those who did not have antibodies to the virus. However, the narrative did not end there. The emergence of advanced variants of the original viral strain has sent shockwaves through the relieved communities. Of these SARS-COV-2 variants, the Delta variations (Delta & Delta plus) are the most transmissible and could delay the onset of herd immunity for many years (Del Rio et al., 2021). Herd immunity refers to a situation when many people in a population get immune to a virus, the infection ceases to propagate and may even diminish (Caldwell et al., 2021, Pillalamarri et al., 2021). The rapid development of the COVID-19 vaccine was undoubtedly a fortuitous occasion, but the emerging variants have challenged the effectiveness the current vaccine. Prior to the breakthrough of the COVID-19 vaccine, the mumps vaccine was the fastest discovery in history (Ullah, 2020a, Cleve, 2021). The Delta variant first surfaced in India in late 2020 and quickly expanded to 100 countries around the world, becoming the dominant strain responsible for the bulk of COVID-19 infection (Cherian et al., 2021). The Delta strain is surging, with case numbers and hospitalizations on the rise all around the world, particularly in countries where vaccina-

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tion rates are low. A recent study suggested that the Delta variant escapes neutralizing monoclonal and polyclonal antibodies induced by previous infection with SARS-CoV-2 or immunization in part, but not entirely. Their neutralization trials show that antibodies generated by the Pfizer and AstraZeneca vaccines are effective against the Delta version, but three to five times less effective than the Alpha form (B.1.1.7) (Planas et al., 2021). As a result, it is vital to recognize the immune response that protects individuals from infection with COVID 19 virus and its variations. While data on the infectivity of SARS-CoV-2 original and mutant strains has been published consistently, there hasn't been a single article that reveals the likely underlying mechanism that allows infected carriers to survive COVID-19 and develop immunity. This investigation could bring us to a hitherto unexplored zone of SARS-CoV-2 infection and lasting immunity. In this study, we look at how SARS-CoV-2 patients can gain a new degree of protection through a putative molecular mechanism. We propose that activation-induced cytidine deaminase (AID), which is catalytically ineffective under normal circumstances, helps enhancing antibody affinity by deaminating cytosines inside immunoglobulins (Ig), thus potentiating the humoral response to SARS-CoV-2 immunogenicity (Gourzi et al., 2006). AID is the enzyme that initiates the first molecular processes to antiviral immunity (Ullah et al., 2017, Gaya et al., 2018, Ullah et al., 2019). We suggest that, considering the rising infection and the emergence of new COVID-19 variations, exploring new strategies to design vaccines, treatments, or agonist compounds is a pressing necessity. Currently, the global immunization effort is in full swing but the fear of reinfection with the new SARS-CoV-2 variants is looming large in people's minds. With all the unknowns surrounding COVID-19, it is evident that our immune system is designed to create effective antibodies against a specific invader. When we are re-infected by the same invader, our immune system quickly recognizes it and defends against it by retrieving prior infections (Gasteiger et al., 2017). Although the usefulness of COVID-19 vaccines in reducing coronavirus transmission has been contested, vaccination has clearly reduced COVID-19 symptoms and serious illness (Kumar et al., 2021, Swan et al., 2021). Based on our present immunology understanding, we can predict that no matter how transmissible a variant is, it will contribute to the development of long-term immunity, eventually leading to perpetual immunity. The innate immune system is an evolutionary conserved host defense system that can sense the invading antigen. As suggested initially, the original SARS-CoV-2 virus (Alpha form) mutates far less than HIV or influenza viruses and is less transmissible. It is now clear that SARS-CoV-2 variants (Delta & Delta plus) could be highly transmissible (Callaway, 2020). Studies have shown that people infected with SARS-CoV-2 Delta are more likely to spread the virus before showing symptoms than those infected with previous versions (Mallapaty, 2021). Even though these new strains are more communicable and infectious, they may help to shape our immune system's evolution. It may take longer than anticipated, but we believe that our immune system will adapt to the new viral strains and will produce a diverse repertoire of immunoglobulins (Ig) which have a stronger affinity to knock down the virus. Studies have demonstrated that activation induced cytidine deaminase (AID) activity could provide answers to such developing tactics since it is involved in initiating programmed DNA modifications that lead to antibody diversity to combat an unlimited variety of infection-causing pathogens (Gazumyan et al., 2012, Ullah, 2020b, Ullah et al., 2021b). Recent reports indicate that individuals infected with Delta had higher quantities of virus particles in their bodies than people infected with the original kind of SARS-CoV-2 suggesting that the variant appears faster and in much higher concentration (Reardon, 2021). Latest data implies that antibodies in COVID-19 stabilized patients will survive up to eight months, while previous literature predicted they will disappear in three months from the time the patients first experienced symptoms (Khan et al., 2020, Wajnberg et al., 2020, Choe et al., 2021). We hypothesize that when more people become infected with either new strains or older versions of the virus and are consistently vaccinated, they will develop a humoral response that will outperform the SARS-CoV-2 virus indefinitely. In addition, recent findings have demonstrated that The Delta variation replicates substantially more quickly than the other variants. Delta infected patients had virus loads that were up to 1260 times greater than those infected with the original strain (Reardon, 2021). We believe that the Delta variation may have influenced some aspects of immunity in persons who received their vaccinations a few months ago. However, this does not imply that our immune system is no longer responding to this new version. Instead, B cells undergo clonal selection until high affinity antibodies are created. This gives credibility to the idea that Delta-infected people's immune systems can eliminate the virus in diverse ways.

We propose that AID is selectively active in Delta-infected patients, promoting an efficient humoral immune response by changing the immunoglobulin genes (Ig) that code for antibodies. The emergence of new SARS-CoV-2 strains has put AID to the test in terms of developing high affinity antibodies capable of neutralizing the virus indefinitely. As a potential innovative treatment target, researchers might concentrate their efforts on antibody formation through AID, which could provide the foundation for lifetime immunity against the virus.

2. AID is a springboard to a robust and long-lasting immune response?

Tasuku Honjo and colleagues identified AID in 1999 and it has since been linked to antibody diversification [23]. Site-specific recombination of variable (V), diversity (D), and junction (J) regions during B cell development results in the diversity of primary antibodies which have a significant impact on immunological responses (Kato et al., 2012, Chi et al., 2020). The process of antibody diversification begins when a patient encounters a certain antigen for the first time. This antibody-antigen interaction not only enables other immune system cells to destroy the infectious organism, but it also improves the antibody's ability to successfully resist infections in later encounters with the same antigen (Kato et al., 2012). By catalyzing the deamination of cytosine, AID initiates the process of antibody diversification, resulting in a uracil: guanine (U: G) mispair (Di Noia and Neuberger, 2002, Feng et al., 2020, Ullah and Akbar, 2020, Ullah et al., 2020). The mispair is subsequently processed by the enzyme uracil DNA glycosylase (UNG), which results in the formation of an abasic site. Finally, as translation polymerases replicate across the abasic site, mutations occur that result in class switch recombination (CSR) and somatic hypermutation (SHM) **(**Fig. 1**)**. These genetic changes result in antibodies that have a higher affinity for the targeted antigen. A clonal selection process generates a new population of antibodies with a greater level of fitness to counter an infectious pathogen.(Sohail et al., 2003, Samaranayake et al., 2006).

Based on previous studies that found a substantial link between AID induction and in vivo antibody affinity maturation (Chaudhuri et al., 2004, Luo et al., 2004), we predict that while the Delta variants (Delta & Delta plus) and other future variants may delay our immune response, they do cause our bodies to develop antibodies that are highly specific for them. Our immune system adapts and broadens its capabilities over time, resulting in a more effective immune response each time we are confronted with the same or a different version of an attacking antigen. The enzyme AID belongs to the apolipoprotein B RNA-editing catalytic component (APOBEC)

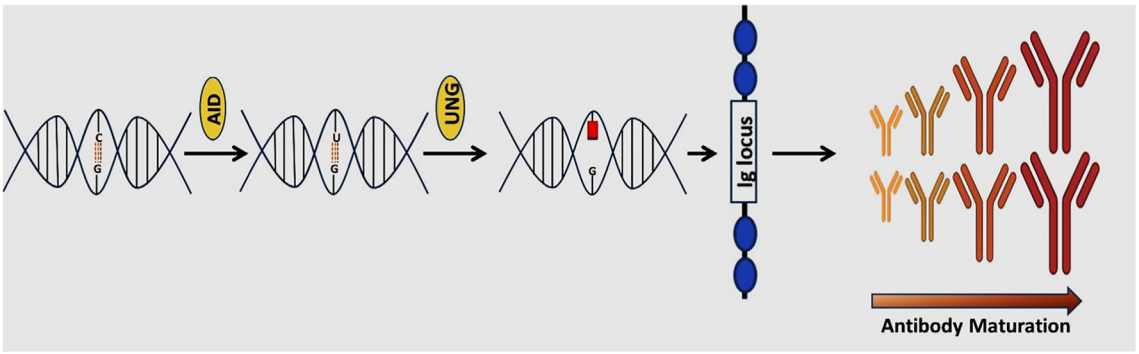

Fig. 1. Consequences of Cytosine (C) deamination by activation induced cytidine deaminase (AID). AID remove amino group from C to produce uracil (U). Upon interception by UNG an abasic site is created causing SHM & SRC of Ig genes.

family, which converts cytosines (C) to uracil (U) in single-stranded DNA (King and Larijani, 2017). The human genome contains eleven APOBEC (apolipoprotein B mRNA editing catalytic polypeptide-like) proteins, which are zinc-dependent deaminases. APOBEC1, APOBEC2, APOBEC3 (including members A, B, C, D, F, G, and H), APOBEC4, and AID are all members of the APOBEC family (Salter et al., 2016). All members of this family have antiviral activity in mammalian cells by inducing lethal editing in the genomes of small DNA viruses, herpesviruses, retroviruses, and RNA viruses such as coronaviruses (Stavrou and Ross, 2015, Ratcliff and Simmonds, 2021). Studies have identified that the SARS-CoV-2 genome features an excess of homoplastic C to U transitions, which is comparable to that induced by cytidine deaminases from the APOBEC protein family (Di Giorgio et al., 2020, Simmonds, 2020, Ratcliff and Simmonds, 2021). The implications of human defensive mechanisms such as APOBEC on SARS-CoV-2 evolution have been intensively researched. SARS-CoV-2 sequence data has indicated instances of directional mutation pressures put on the SARS-CoV-2 genome by host antiviral defense systems (Di Giorgio et al., 2020, Poulain et al., 2020, Vlachogiannis et al., 2021). Based on these findings, as well as the previously documented involvement of AID in B cell tolerance and antibody development, we hypothesized a plausible mechanism for the humoral immune response to SARS-CoV-2 infection. The formation of high affinity antibodies in COVID-19 patients, we believe, has far-reaching implications for new therapy targets and vaccine development. As we write this article, 32.4 percent of the global population has received at least one dose of a COVID-19 vaccine, and 24.4 percent is completely immunized. Globally, 4.93 billion doses have been administered, with 34.25 million administered each day (https://ourworldindata.org/covid-vaccinations). With so much success, the appearance of the novel SARS-CoV-2 Delta strain has experts wondering if new mutations could compromise the efficacy of current vaccines. It is vital to uncover new targets and delineate immune pathways to combat the coronavirus onslaught (Akbar et al., 2021, Ullah et al., 2021a, Ullah et al., 2021c). It is worth noting that we are heading toward herd immunity, which could lead to a perpetual immunity; nevertheless, in the meantime, in addition to vigorous immunization, there is an overwhelming need for new choices for COVID-19 treatment. Finally, there is always a threat of a SAR-CoV-2 variant(s) that might evade our protection from vaccines and overthrow our efforts. Evidence is mounting that the vaccines approved for Covid are successful in saving lives and keeping people out of the hospital. Mutant strains such as Delta and Delta plus have already dampened the impact of antibodies that are critical for fighting the illness. Vaccinating people is the most efficient strategy to reduce the threat of emerging viral strains. Before scientists can create a universal vaccination that can protect against all strains of the virus, they must first uncover new therapeutic targets that can trigger or modify an immune response in a way that either preserves or restores the desired immunity. In this quest, we believe that AID, as a mutator enzyme that targets immunoglobulin (Ig) genes, could be a viable novel therapeutic target.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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