Real Concerns over COVID-19 Variants of Concern

Hatem Tallima, Rashika El Ridi*

Zoology Department, Faculty of Science, Cairo University, Giza 12513, Egypt

Address correspondence to: Rashika El Ridi, Zoology Department, Faculty of Science, Cairo University, Giza 12613, Email:rashika@sci.cu.edu.eg.

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INTRODUCTION

Severe acute respiratory syndrome corona virus (SARS-CoV)-2 obtained from patients infected despite being fully vaccinated with either BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), or JNJ-78436735 (Janssen) showed increased mutations rates in the N-terminal domain (NTD) and receptor-binding domain (RBD) of the spike glycoprotein when compared with virus from unvaccinated controls (1). These changes are associated with immune evasion and diagnostic failures, prominent characteristics of variants of concern (2). Variants of concern (VOC) appeared to be overrepresented in numerous breakthrough infections of fully vaccinated people in the United States and (1, 3-6), and Israel (7). These findings confirm concerns about the relation of SARS-CoV-2 variants with vaccine breakthrough, and urged us to attempt clarifying the likely link between vaccination with the currently used vaccines and VOC emergence.

VIRUS REPLICATION IN IMMUNE CELLS

Upon invasion of the nasopharynx and oral cavity, SARS-CoV-2 may be opsonized by complement components or antibody, and engulfed in immune cells, such as neutrophils, macrophages, and dendritic cells. The virus is endocytosed in the immune cells to be digested by endosomal or cytosolic enzymes, and peptides processed for presentation on the surface membrane, in association with HLA class II and class I molecules, ready to stimulate the generation of specific antibodies and cytotoxic T cells, while virus replication is abortive (8).

VIRUS REPLICATION IN STRUCTURAL CELLS

SARS-CoV-2 accesses epithelial cells in the tongue, salivary glands, and mucosal lining of respiratory and digestive tract via binding to the host cell receptor, angiotensin-converting enzyme 2 (9, 10). Virus load invading structural cells is met by the cytoplasmic innate immunity receptors, notably retinoic acid-inducible gene-I (RIG-1). Upon interaction with the viral genome, RIG-1 abrogates its very first replication steps, resulting into abortive infection (11, 12). Failure of the innate defense mechanisms (13) allows viral replication to completion, transport of the virions to the cell surface and release by exocytosis, usually followed by cell death apoptosis, necroptosis, and pyroptosis (9, 14-16).

IMMUNE RESPONSES IMPACT ON VIRUS REPLICATION IN STRUCTURAL CELLS OF UNVACCINATED HOSTS

Before and concomitantly to virus multiplication in host structural cells, antibodies to viral proteins and glycoproteins are generated, and assist in preventing virus entry in more cells via agglutination, opsonization, complement activation, and neutralization of virions. Antibodies may also assist natural killer cells and macrophages in antibody-dependent cell-mediated cytotoxicity (ADCC) of infected cells displaying viral peptides on their surface membrane. Widespread lysis of such cells is achieved by cytotoxic T lymphocytes (17). Subsequent virus spread, release of danger-associated molecular patterns (DAMP), severe inflammatory reactions, and fulgurant cytokine storm affect the infected host. Lysis of virus-infected cells anytime in the midst of virion replication, virion assembly and exocytosis processes leads to the release of mature, immature, aberrant, and **variant** virions, which may threaten populations around (18-21). Such events, however, took place in only a fraction of the 200 million SARS-CoV-2 infected people, because the vast majority therefrom was able to restrict the infection, essentially relying on their efficient innate immunity responses (13, 17, 22-24). Importantly, most, if not all, the 20 million worldwide who suffered severe disease (25) were hospitalized, confined, isolated, and prevented from delivering current or variant virions to the surrounding environment and people. Notwithstanding, several SARS-CoV-2 variants of interest and VOC emerged (26-28).

IMMUNE RESPONSES IMPACT ON VIRUS REPLICATION IN STRUCTURAL CELLS OF FULLY VACCINATED HOSTS

Immunization with the vaccines in world-wide trials (17) leads to generation of cytotoxic T cells specific to viral peptides in association with HLA class I molecules, and specific antibodies capable of mediating ADCC of cells that display relevant viral peptides on their surface. Upon SARS-CoV-2 infection of structural cells in the nasopharynx, memory cytotoxic T cells as well as antibodies are rapidly generated, bypass innate immune defenses, and besides hindering virus movement, they immediately proceed to killing of infected cells, not at the onset of replication of the viral genome, as for RIG-1, not at the completion of virion assembly as in unscathed cells, but anytime in the midst of the multiplication processes, entirely unpredictably and at random, generating the release of mature, immature, aberrant, and **variant** virions. Such events may take place in more than two billion vaccinated people who are living free of confinement and lockdown since they suffer only mild disease or are asymptomatic (1-6; 25, 26, 29). The enormity of the number of individuals inoculated with the vaccines, continuous exposure to SARS-CoV-2, (1, 3-7), and energetic outdoors activities will centuplicate **the probability** of acquired immunity-generation and spread of further VOC (1-7).

DISCUSSION

The mounting immune pressure of humans led the SARS-CoV-2 virus to evolve variants less susceptible to antibody-mediated neutralization (29). Hence, access to the host structural cells is still permitted. Entry into immune cells is also preserved via complement activation, agglutination, and opsonization. Acquired immunity is fully activated leading to generation of antibodies, which fail to protect the host, yet synergize via ADCC with cytotoxic T cells to destruction of all cells harboring virus and expressing viral peptides on the their surface membrane, with release of immature and aberrant virions. The virus suffering from the

inability of properly replicating may evolve or variant virions may emerge that preferentially, directly and rapidly target the immune-privileged sites of the brain, the anterior chamber of the eye, heart valves, and testes (30-33). It is best that humans never face such variant, which indeed should be named the omega (ω) variant. Accordingly, it is recommended to refrain from using the available vaccines (34, 35) and only rely on the spike glycoprotein subunit 1 in a protein form (17) for vaccination of individuals with underlying morbidities, advanced age, and at serious risk.

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