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Importance of glycosylation for SARS-CoV-2 virus, antibodies and COVID-19

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Abstract

In addition to the known endemic respiratory viruses, the pandemic SARS-CoV-2 has been added, with terrible effects on the population worldwide. This virus, like many others, has a glycoprotein structure the so-called spike protein, which interacts with the ACE-2 receptor as a cellular entry gate and thus initiates the infection. Just as this glycosylation causes infectiousness, the effect of the protective antibodies is also determined by their degree of glycosylation. In particular, the so-called Fc part of the immunoglobulins plays an important role. The type of bound sugar such as fucose, mannose, sialic acid, etc. determines, among other things, which reactions are triggered by binding to immune cells such as NK cells to their existing Fc receptors. These include antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular trogocytosis (ADCT) and antibody-dependent cellular complement deposition (ADCD). In addition to protective phagocytosis, these reactions can trigger the antibody-dependent enhancement (ADE) of the infection and also the dreaded cytokine storm in COVID-19 patients. The functional diversification of IgGs by Fc glycosylation can be determined and tracked both after vaccination and during the disease.

Keywords: *SARS-CoV-2, COVID-19, antibody glycosylation, IgG glycosylation, glycomics, biomarkers.*

Introduction

The current global coronavirus pandemic 19 (COVID-19), caused by the novel coronavirus (SARS-CoV-2) and its variants, has led to extensive hospitalizations worldwide [1]. To date, more than 253 million infected people and more than 5 million deaths have been reported [2]. The seasonal cycle of respiratory viral diseases has long been widely recognized, as annual epidemics of influenza and colds hit the human population like clockwork in the winter season in temperate regions. (See Figure 1):

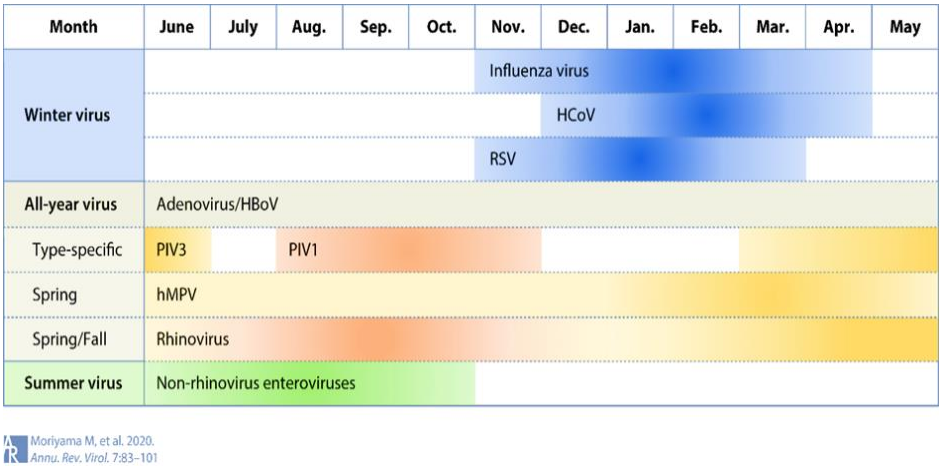

Fig.1: Influenza virus, human coronavirus and human respiratory syncytial virus (RSV) show clear peak incidences in the winter months, which is why they are sometimes referred to as winter viruses. To [3]

The four endemic human coronaviruses HCoV-229E, -NL63, -OC43 and -HKU1 contribute a significant proportion of upper and lower respiratory tract infections in adults and children [4,5] In addition, epidemics caused by SARS-CoV-1 and the newly emerged SARS-CoV-2 occur during the winter months [3,6]. However, whether this can lead to viral interference in the sense of excluding a "tripledemic" seems likely.

SARS-CoV-2 and other respiratory viruses often "interfere" with each other. The COVID-19 pandemic has been associated worldwide with changes in respiratory virus infections that differed between virus types [7-9].

The decline in respiratory virus infections, including influenza viruses and respiratory syncytial virus (RSV), was most notable at the beginning of the COVID-19 pandemic and continued to varying degrees through subsequent waves of SARS-CoV-2 infections [10, 11].

A meta-analysis and systematic review showed that up to 19% of patients with COVID-19 co-infections and 24% with super-infections have infections [8]. The presence of co-infection or superinfection was associated with poor outcomes, including increased mortality [8].

The Coronaviridae (coronaviruses) are a long-known family of enveloped single (+) strand RNA viruses (ss(+)RNA [12, 13]. SARS-CoV-2 is a enveloped virus and the SARS-CoV-2 spike (S) protein mediates virion binding to human cells through its interaction with the ACE2 cell surface receptor and is one of the main immunization targets. The receptor binding domain (RBD) is a critical component of the S-protein subunit (S1) that binds to angiotensin-converting enzyme 2 (ACE2), a recognized receptor for virus entry.

Most mutations occur in the spike (S) protein [14], a surface glycoprotein that plays a crucial role in viral infection (Figure 2).:

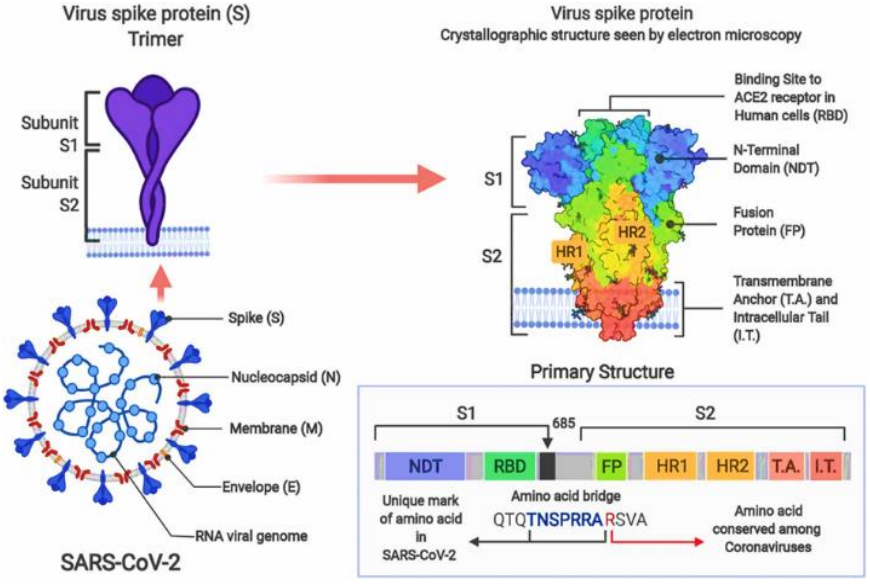

Fig 2: Structure of SARS-CoV-2. Diagram showing the single-stranded RNA genome and proteins present in the coronavirus, as well as the primary and 3D structure of the spike protein. (Adapted from "An in-depth look into the structure of the SARS-CoV-2 spike glycoprotein" by Biorender.com)

Glycosylation of the receptor binding domain of the spike protein of SARS-CoV-2 and the ACE2 receptor leads to stronger and more far-reaching binding interactions between the proteins [15-18]. This also applies to all virus variants. [19].

The viruses use the host cell machinery to glycosylate their own proteins during replication [20]. These viral host cell-derived glycans facilitate various structural and functional roles, from immune evasion by glycan shielding to enhancing immune cell infection [16, 20-22]. With regard to the role of SARS-CoV-2 glycosylation in viral replication, infectivity and immune response, glycosylation has major potential implications for therapeutic and vaccination strategies as well as serological testing [23]. Historically, the role of glycosylation in the dichotomous immune system has always been the focus of research [24-29]. The innate and adaptive immune response [30] in which glycosylation both plays a protective role and contributes to immune evasion by masking viral polypeptide epitopes and contributing to the cytokine cascade via non-fucosylated IgG, interact with a pronounced glycan epitope on the SARS-CoV-2 spike protein. Glycosylation is the most common and complex post-translational protein modification. In addition to proteins, many lipids are glycosylated, and only recently it has been shown that elaborated

glycan structures can also be bound to RNA [31], as shown schematically in the following figure:

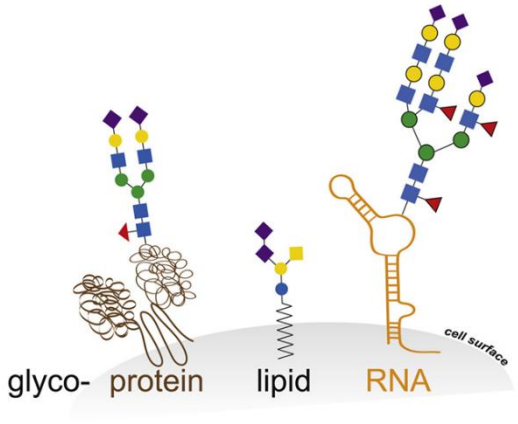

Fig 4: Glycoprotein. Glycolipid and glycoRNA (according to [31])

The most intensively studied example of Importance of alternative protein glycosylation for biological functions are immunoglobulins [32,33], which are among the main weapons of humoral immunity. Immunoglobulin G (IgG) antibodies play an important role in the immune response against SARS-CoV-2. Antibodies are Y-shaped molecules (see Fig. 5, 6). In the past, research on humoral responses to viral infection focused mainly on the V-end of the Y: the antigen binding regions, or Fab (fragment antigen binding). Conversely, the tail of Y (also known as fragment crystallizable or Fc domain) has numerous effector functions, such as antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular trogocytosis (ADCT) and antibody-dependent cellular complement deposition (ADCD). Antibody-dependent enhancement (ADE) also takes place via FCγR:

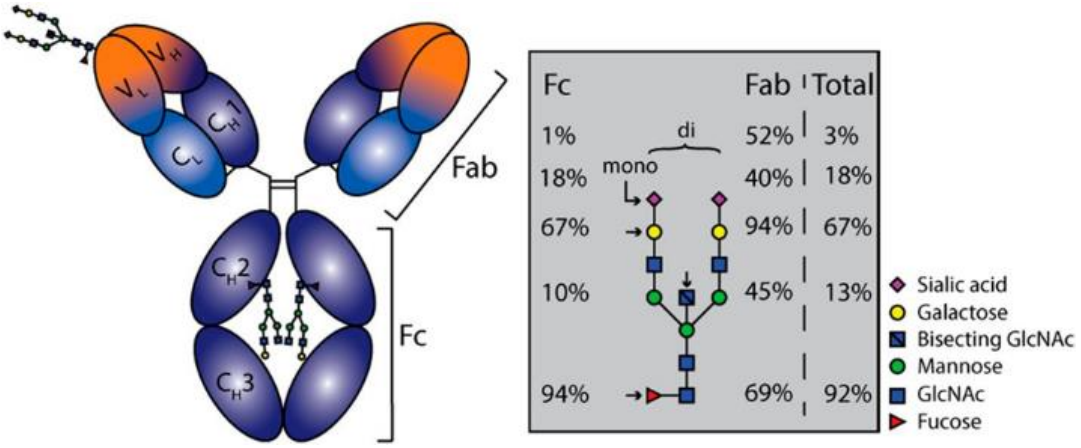

Fig 5: Structure of IgG and the IgG N-linked glycan (according to [33])

Since the effector functions of IgG are modulated by N-glycosylation of the Fc region, the structure and possible function of the IgG N-glycome in relation to divergent COVID-19 disease courses was investigated [24, 34-38].

Although immune responses in humans generally produce fully fucosylated IgG [38-42], some antigen-specific IgG responses may be predominantly afucosylated. The consequences of afucosylated reactions vary depending on the setting. Afucosylated antigen-specific IgG leads to immunopathology in SARS-CoV-2 [43-46] and dengue virus infections:

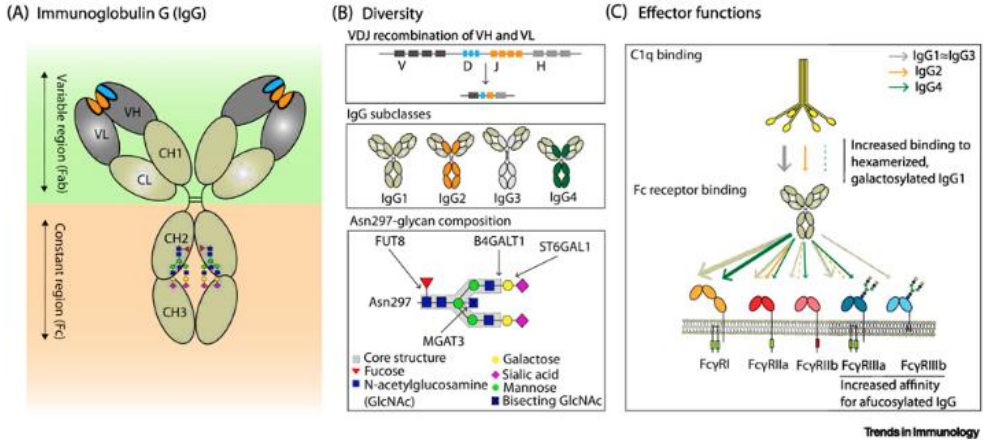

Fig 6: Diversity and effector functions of human IgG (according to [47])

Changes in galactosylation, fucosylation and sialysation are now well-established factors driving differential IgG function, ranging from inhibitory/anti-inflammatory to activating complement and promotion of antibody-dependent cellular cytotoxicity (ADCC).

Fc receptors (FcR) are expressed on immune cells and bind the Fc portion of immunoglobulin. Fcγ receptors (FcγR), the largest group of FcR, bind IgG and include several subtypes [48,49].

Antibody effector functions such as the ADCC, ADC and ADCD play a crucial role in immunity against several pathogens, especially in the absence of neutralizing activity. Two modifications of the IgG constant domain (Fc domain) regulate the effector function of immunoglobulins: changes in the antibody subclass and changes in a single N-linked glycan located in the CH2 domain of IgG Fc (Fig.6).

The addition of different glycans can significantly alter the conformation of the Fc, with dramatic consequences for the IgG effector functions as Figure 7 shows [50]:

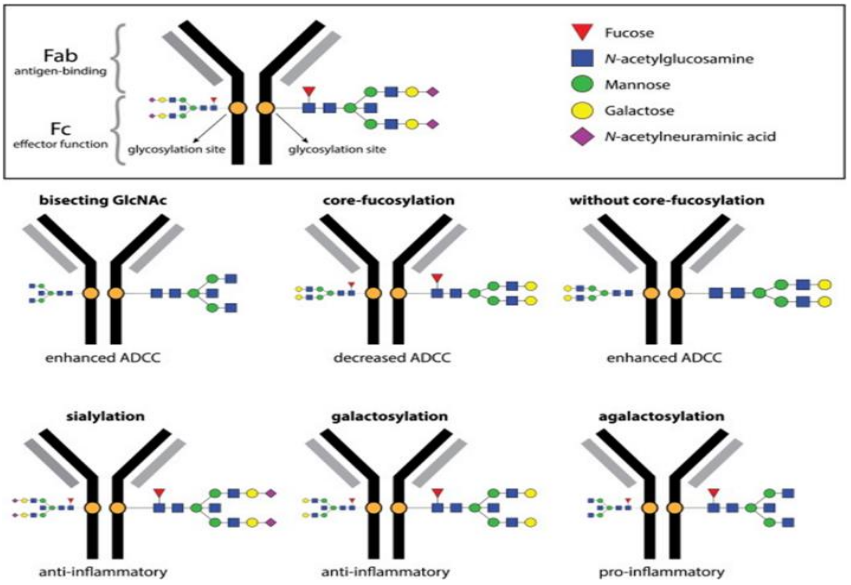

Fig 7: Functional implications of alternative glycosylation of IgG. (After [50])

This astonishing phenomenon that both SARS-Cov-2 and the immune cells involved use post-translational glycosylation, on the one hand to penetrate the cells more easily and thereby "mask" themselves or to make the humoral response to the infection more effective, speaks for the evolutionary interdependence. It is therefore not surprising that immunoglobulin G glycans have been measured as an early indicator of the severity of COVID-19[36, 37, 51] and can be used to monitor the disease [52]. The decoding of glycosylation processes by high-throughput glycomics and proteomics open up future perspectives that explain pandemics from zoonotic origins to the mechanisms of infectious diseases in a well- founded way. [53-57].

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