Commentary

Christ Bearing the Cross: The Original Antigenic Sin of the Immune System and Its Potential Role in Emerging Diseases

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When a new infectious disease emerges, memory cells from previous exposure to a related, but different, micro-organism may become activated. This phenomenon has been termed the original antigenic sin. When the induced antibodies against the related micro-organism would be not functional, the original antigenic sin would impair the effectivity of the primary response. Otherwise, the sin would turn out to be a virtue because the memory response would contribute to the elimination of the emerging infectious disease.

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Preface

In the 27th chapter of the gospel of Matthew, in the New Testament of the Christian Bible, the trial and crucifixion of Jesus is described. On his way to Calvary, Simon of Cyrene helped Jesus carrying the cross. When they stopped for a moment on the Via Dolorosa, a woman by the name of Veronica, used her veil to wipe the sweat and blood from the face of Jesus. The image of the face of Jesus afterwards appeared to be imprinted in the veil. This remarkable scene, however, is not described in the Bible, but first appeared in the book Meditations on the Life of Christ in the 13th century [1] The scene is depicted in the painting of Hieronymus Bosch on one of the outside panels of The Temptation of Saint Anthony, named Christ Bearing the Cross (Figure 1a). Veronica with the veil is clearly shown, but like any painting that shows an action, it is frozen in time and therefore doesn't reveal whether the scenery is before or after Jesus has cleaned and dried his face.

 doi.org/10.32388/UWC636

Christ Bearing the Cross also is the title of another painting that first also was ascribed to Hieronymus Bosch, but after technical inspection now is considered to be the product of a follower [2]. The detail of that painting in Figure 1b shows Christ and Veronica, amidst a crowd of people, who, based on their hostile caricature faces, probably are not followers. Veronica is holding her veil with the imprint of the face of Jesus. When comparing the face of Jesus with the imprint, the similarities are obvious but also clear differences can be seen, in the eyes (open or closed) and beard for instance. The imprint of the face is not perfect, but clearly an artist impression. It can be envisioned that Veronica, at a later moment in her life when looking at her veil with the imprint, will recall the face of Jesus.

Figure 1.

Panel a: Detail of Christ Bearing the Cross. Outside panel of The Temptation of Saint Anthony by Hieronymus Bosch, 1500-1510, Museu Nacional de Arte Antiga, Lisbon, Portugal. Source: https://commons.wikimedia.org/wiki/File:Workshop_of_Jheronimus_Bosch_-_Temptation_of_Saint_Anthony_(closed).jpg Assessed June 17, 2023.

Panel b: Christ Bearing the Cross. Follower of Jheronymus Bosch, Museum of Fine Arts, Ghent, Belgium. Source: https://commons.wikimedia.org/wiki/Jheronimus_Bosch#/media/File:Hieronymus_Bosch_055.jpg Assessed June 17, 2023.

Imprinting and the original antigenic sin in infection and immunity

The recall of imprinted immunological memory by a novel antigen of an emerging virus, which differs from the original stimulating antigen is a phenomenon called original antigenic sin. This term was coined by Thomas Francis Jr. in 1960, with reference to the original sin committed by Adam and Eve. According to the Bible, the original sin is passed on to all future generations. The basis for the original antigenic sin thus is imprinting: imprinting of the original antigen into the immunological memory. These memory T- and B-lymphocytes, and all of their future generations, are activated by renewed contact with the same antigen, but can (also) be activated when exposed to a variant of that antigen, expressed by an emerging virus. This can be considered a sin, because recognition of antigen by antigen receptors on B- and T-lymphocytes is supposed to be specific.

The concept of the original antigenic sin (OAS) was based on the observation of Francis that influenza antibody titers, as determined in a hemagglutination inhibition assay, were highest against those influenza strains to which specific age cohorts had first been exposed. [3][4]. The phenomenon of OAS has also been proposed as explanation for recurrent infections with the same pathogen such as dengue [5][6], and it has been suggested for HIV and SARS-CoV-2 [7].

The first generation of Respiratory Syncytial Virus (RSV) vaccines consisted of formalin-inactivated alum-precipitated RSV. When this vaccine was used in RSV-naïve infants, who later became naturally infected with RSV, many children developed severe respiratory disease, in some cases fatal [8]. This has been interpreted as OAS [9], but antibody dependent enhancement (ADE) is more likely to have occurred. A negative effect of vaccination also has been documented for a corona vaccine, not for human use but for prevention of feline infectious peritonitis virus. Vaccinated animals developed high titers of virus neutralizing antibodies, but upon challenge with live coronavirus they were not protected but even more vulnerable than the non-vaccinated control animals [10] These findings could be interpreted as OAS, but also are more suggestive for antibody-dependent enhancement (ADE) [10].

Original antigenic sin and SARS-CoV-2 variants

Imprinting of an original antigen into immunological memory, and the consequences for future responsiveness to variants of the original antigen also has been and still is debated in the context of the COVID-19 pandemic [11]. This especially relates to the effectiveness of booster vaccination with updated

vaccines such as the bivalent vaccines containing both the mRNA encoding the S1 spike protein of the ancestral WA1/2020 strain of SARS-CoV-2 as well as that of future (omicron) variants.

It has been suggested that prior exposure to antigens shared between SARS-CoV-2 and existing seasonal human coronaviruses (hCoVs) including beta coronaviruses (hCoV-OC43 and hCoV-HKU1) and alpha coronaviruses (hCoV-NL63 and hCoV-229E) could have a negative effect on the outcome of infection or vaccination [12]. Vaccination with SARS-CoV-2 (mRNA) vaccines caused an increase in IgG antibodies against the beta coronaviruses hCoV-OC43 and hCoV-HKU1, but not against alpha coronaviruses [13]. Such a phenomenon, related to OAS, is termed back boosting of memory. Other have found the opposite, namely that SARS-CoV-2 infection causes an increase in beta coronaviruses, but mRNA vaccination does not [14]. We have studied the IgG (and IgA) anti-SARS-CoV-2 antibody response in COVID-19 patients, either admitted to the ICU or the general COVID-19 ward [15]. While in both groups of patients a significant SARS-CoV-2 antibody response was observed, we found minimal and inconsistent fluctuations in IgG against hCoV-OC43, hCoV-HKU1, hCoV-NL63, and hCoV-229E. These data indicate that the anti-SARS-CoV-2 antibody responses were not the result of cross-reactivity due to a previous common hCoV infection [15].

Many papers, with viewpoints and speculations have been published on OAS in the context of bivalent (and multivalent) SARS-CoV-2 vaccines. The first actual data on bivalent mRNA vaccines show that booster vaccination with bivalent Omicron BA.4-BA.5 mRNA vaccines induces marginally better VNT against relevant Omicron variants than booster vaccination with monovalent ancestral WA1/2020 strain SARS-CoV-2 mRNA vaccine [16][17]. This can be interpreted as OAS [18], although it has to be admitted that an additional group which is booster vaccination with monovalent Omicron BA.4-BA.5 mRNA vaccine would have made the interpretation of these data more straightforward. It has been reported that in people vaccinated with the WA1/2020 strain who subsequently contracted an Omicron infection, cross-reactive antibodies to both strains were found. In non-vaccinated people, Omicron infection induces mainly Omicron specific antibodies [19]. The ultimate antibody response, as well as levels of imprinting, appears to depend on the number of boosters and also on the infection history, resulting in what has been termed hybrid immune damping [20].

What is the sin, and is it a sin?

Since the first publication of Thomas Francis, many other studies have been published on repeated influenza vaccination. The outcome of those studies is highly variable, with some studies being indicative for OAS and others not [21]. The hemagglutination inhibition (HI) assay, the in vitro technique for measurement of anti-influenza antibodies, is not a truly functional virus neutralization test (VNT), despite the fact that HI and VNT titers correlate [22]. A further point of consideration regarding the underlying mechanism of OAS are the potential differences in the affinity of the antibodies generated. Antibodies against epitopes of the original virus strain, which will be derived from memory B-lymphocytes have a higher affinity. This could result in an advantage when competing for binding to antigen. Data from B cell fate-mapping experiments however show that secondary germinal centers (GCs) are composed for over > 90% of naïve B-cells [23]. This implies that there would be no competition for antigen between the higher affinity BCR of memory B-lymphocytes with the germline BCR on naïve B-lymphocytes [23]. In additional experiments, using B cell fate-mapping with the same influenza strains which formed the basis for the concept of OAS (A/Puerto Rico/8/1934 and A/Fort Monmouth/1/1947), the findings of Thomas Francis Jr could not be reproduced [24].

The “sin” of the immune system, reactivation of existing memory by variants of the original antigen, not necessarily has to be interpreted in a negative way. Therefore alternative names for OAS have been used recently, such as “primary addiction” [24] and “hybrid immune damping” [20], or just ”imprinting” [25]. Whatever term for the OAS eventually will surface, the mechanisms of the phenomenon remain to be fully elucidated. At any rate it is of prime importance to closely monitor the immune response and efficacy of repeated vaccination against micro-organisms such as SARS-CoV-2, with ongoing variation in their major antigens. For now it can be concluded that vaccination with WA1/2020 strain based vaccines in the USA alone have prevented 18 million hospitalizations and 3 million deaths which otherwise could have been caused by alpha, beta, or omicron variants of SARS-CoV-2 [26]. As long as boosting of imprinted memory against previous SARS-CoV-2 variants (either induced by natural exposure or by vaccination) does not impair the primary response to novel variants, OAS is not a sin but a virtue..

Abbreviations

- ADE: antibody-dependent enhancement
- BCR: B cell receptor

- COVID-19: corona virus disease 2019
- HI: hemagglutination inhibition
- OAS: original antigenic sin
- SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
- VNT: virus neutralization titer

Declarations

Author contributions

GT and FO: Conceptualization, Writing-original draft, Writing-review & editing. Both authors read and approved the submitted version."

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.