Correspondence

COVID-19 induced autoantibodies are directed against an enormous number of disease-related autoantibodies: the SARS-CoV2 autoantigen-ome era

Running title: Autoantibodies and autoantigen in COVID-19

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Abstract
Autoantibodies are frequently induced during SARS-Cov-2 infection, especially in patients suffered from sever COVID-19. The prevalence of autoantibodies ranges amongst studies but there is a consensus regarding the antigen-specificity of the observed humoral responses. These autoantibodies appear to be directed against known autoantigens, several of which are associated with organ and non-organ specific diseases, while others have not been previously considered significant triggers of autoimmunity and overt autoimmune disease. In this letter, we comment on a recently published study underlying the universal role of SARS-CoV-2 infection as an instrumental initiator for autoantibodies potentially directed against hundreds of autoantigens, several of whom are predictors of future development of an autoimmune diseases. Of pathogenic relevance, the findings of that study undescore a novel pathway used by the virus to initiate autoimmunity and indeed autoimmune disease.

Dear Editor,
I.   INTRODUCTION
It is well know thar persistent viral infection is a likely trigger of autoimmunity and autoimmune diseases. Epidemiological studies, serological and cellular findings, virological data and findings stemmed from experimental models of autoimmune diseases are supporting this notion, irrespectively of the causative viral trigger or the nature of the autoimmune disease. Early days, several investigators have attempted to provide evidence in support of a direct effect of viral infection in provoking autoimmunity. An example that this machinery is that placing the virus as an instrumental cause of apoptosis of infected cells. Such apoptosis may serve as the impetus for the release of neo-antigens or the relevation of cryptic epitopes. Such a release, in concert with the inflammatory process due to chronic infection, can be sufficient for immunological breakdown and subsequent tissue destruction and organ impairment.

Another mechanism, which has been considered a likely trigger each time a pathogen is linked to autoimmunity is that of molecular mimicry. We and others have produced a wealth of data at the clinical setting in support or against the evidence of that mechanism (1-8). We postulated that specific viruses or microbes are indeed likely triggers of organ specific disease such as those inficting damage to the liver and we have been able to describe pathogen/self mimicking sets of antigenic peptides targeted by cross-reactive humoral and cellular responses in patients at early stages of the disease. Such data have also been obtained by others. Data of such kind have also been described in animal models of the relevant autoimmune diseases.

In the case of COVID-19 related autoantibodies a plethora of published studies have attempted to associate SARS-CoV-2 with autoimmunity, *via* molecular mimicry and immunological cross-reactivity but most of these studies with few excemptions have limited their investigations in the description of amino acid homology sets of SARS-CoV-2 and self protein mimics (9). Such a desciption does not represent clear evidence of the existence of molecular mimicry as most of the relevant sets are totally unreactive and by no means relate to true "antigenic mimicry"(7). Moreover, the presence of immunologal cross-reactivity in COVID-19 patients with detectable autoantibodies does not necessarily means that SARS-CoV-2 is the prime mover of the de novo appearance of autoantibodies as it could be epiphenomenal or short lived (9).

A recent study by Wang et al (10) has attempted to provide an holistic new view of the link between SARS-CoV-2, COVOD-19 and autoantibody/autoantigen saga. These authors have placed SARS-CoV-2 in the epicentre of autoantibody development studying the autoantigen-ome of the virus. During infection and in a attempt to survive and arguably to avoid the host's immune-mediated elimination, the virus manipulates its machinery in such a manner that at the end the host's immune response is rather controlled. Attempts of the host to inititate innate and adaptive immunity, whcih could control and preferably eradicate the virus are universal failures. Not only that, but in most cases, intense attempts of the virus to accelate its defensive immunity may indeed provoke cell apoptosis of the host cells, tissue damage and organ failure. In a sense the host destroys its self in a selpf perpetuating manner. A symbiosis between the virus and self is a comprise that the host must accept to survive. According to the authors this sophisticated host-virus symbiosis is achieved by a broad series of significant alterations of host molecules and the reprogramming of host molecular networks, which are perplexed but interconnected in nature. It appears that the infected host cells can/must/do really experience an extreme stress (10). This leads to ther death and the release of neo-antigens, which provokes a perpetuation of immunological phenomena ultimetaly leading to autoimmunity in the form of de novo appearance of autoantibodies.

The investigators have previsouly noted that in response to the virus, the host (amongst others) synthesizes dermatan sulphate (DS), a molecule which participates in wound healing, tissue repair and dead cell clearance (10). This has been instrumental for their research platform and the fruitful completion of their research projects (11). Why? Because DS appears to show high affinity for autoantigens originated from apoptotic cells and host molecules holding peculiar DS-affinity have an excessive predisposition to develop autoantigenic properties. Hence, the use of a platform based on autoantigen-DS affinity studies can eventually lead to the disvovery of a vast number of novel autoantigens (11).

Using this approach the authors have revealed an incredible number of autoantigens targeted by SARS-CoV-2 inititated immune responses (10). Amongst their 751 member autoantigen-ome, 88% are profoundly altered by SARS-CoV-2 infection, either upregulated, downregulated or both (10).

According to the investigators, 369 proteins (56% of their total DS-affinity proteins) are known autoantigens. This has let the authors to logically assume that COVID-19 is a disease, which can potentially provoke autoantibody production and autoimmune disease development (10). A meticulous assessment of their findings is clearly supporting this notion. Forty-two of their autoantigens relate to myelin sheath and could be likely triggers of multiple sclerosis-related autoantibodies or autoantibodies associated with other autoimmune neurological disorders. In a similar vein, 11 autoantigens are originated from stress fibers and 25 are associated with myofibrils, a feature which could explain several "paradoxical" features of COVID-19, from the appearance of anti-smooth muscle antibodies to the development of various muscular and cardiomuscular features of COVID-19, even in the case of less severe patients (10).

II. CONCUSIONS

In conclusion, the provocative data provided by the study of SARS-CoV-2 autoantigen-ome is intriguing (10) and add support to the notion that this is an "autoimmune virus" (12, 13). It remains to be seen whether the gigantic extent of millions of infections may inflect an increase of the incidence and the prevalence of autoimmune disease in the years to come (14).

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