Coronavirus-induced autoimmunity

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1. Introduction

Several studies have highlighted the link between viral infection and the development of autoimmunity [1-4]. Autoimmune diseases (AID) are characterized by the breakdown of immune tolerance and the activation of self-reactive lymphocytes. Many AID are multifactorial, involving both genetic and environmental factors, such as viral infections. Viruses represent the major environmental factor that triggers the development of autoimmunity in genetically susceptible individuals. There are multiple mechanisms by which viruses can induce an autoimmune reaction, including molecular mimicry, epitope spreading, bystander activation, the presentation of cryptic antigens, B-cell polyclonal activation, and viral superantigens [2, 4-7]. Many viruses have been suspected to trigger or exacerbate AID. The best examples of viruses inducing the development of AID are coxsackie virus, cytomegalovirus, Epstein Barr virus, and hepatitis B virus [2, 3]. We focus here on findings showing that coronavirus appears to also be associated with autoimmunity.

2. Animal model systems

Coronaviruses cause diseases in a variety of species of animals, including humans. The pathogenesis and organ tropism of murine hepatitis coronaviruses (MHV) depends on the viral strain [8]. Neurotropic MHV strains (JHM and A59) have been the most frequently studied [8]. They induce encephalomyelitis, with demyelination, and serve as one of the few animal models for multiple sclerosis (MS)-like diseases. The role of coronaviruses in the development of autoimmunity has come from experimental studies in animal models. Murine coronavirus infection can induce autoreactive T-cells, B-cell polyclonal activation, and autoantibody production.

Experimental autoimmune encephalomyelitis

Watanabe et al. first reported that infection in Lewis rats with the murine coronavirus JHM can induce an autoimmune response. Lymphocytes from Lewis rats infected with murine coronavirus are sensitized to myelin basic protein and adoptive transfer of these lymphocytes leads to experimental allergic encephalomyelitis (EAE)-like lesions in recipient Lewis rats [9]. Mice infected with MHV 2.2-V-1 develop an immune-mediated demyelinating encephalomyelitis and Pewe et al. showed that the CD8 T cell-mediated demyelination is dependent on Interferon gamma (INF-γ) in MHV-infected mice [10]. Furthermore, MHV-4-

infection can also induce an autoimmune T-cell response in mice [11]. Infection with murine coronavirus can also induce the production of autoantibodies.

Experimental coronavirus retinopathy (ECOR)

Experimental coronavirus retinopathy (ECOR) was created in the 1990s [12]. The pathogenesis of this experimental retinal disease is based on three components, a viral component, genetic background, and an immunological component [12]. This degenerative retinal disease is characterized by an early phase, with retinal vasculitis and perivasculitis, and a late phase, with degenerative retinal disease [12]. The pathogenesis of MHV-induced retinal degeneration in BALB/c mice has been shown to be related to autoimmunity, with the presence of antiretinal autoantibodies and anti-retinal pigment epithelial-cell autoantibodies [13]. Two autoantigens, α fodrin and villin 2, have been identified in ECOR [14]. Furthermore, the CD4 T cells from MHV-infected BALB/c mice are specifically activated by α fodrin [14]. MHV strain 59 (MHV-59) is a coronavirus that triggers various pathologies in susceptible mice, such as hepatitis, thymus involution, polyclonal B lymphocyte activation, and, after intra-cerebral inoculation, transient demyelination [5, 15].

Anti-erythrocyte autoimmunity

Mice infected with MHV-59 and immunized with rat-blood erythrocytes develop high levels of anti-erythrocyte autoantibodies. In contrast, the authors observed only moderate autoantibody production by noninfected mice solely immunized with rat-blood erythrocytes, suggesting that the autoimmune response may be enhanced by MHV-59 infection [5].

Mathieu et al. identified two liver proteins, fumarylacetoacetate hydrolase (FAH) and alcohol dehydrogenase (ADH), recognized by autoantibodies in the sera of MHV-A59-infected mice [16]. The same authors then explored the cross-reaction between FAH and MHV proteins. The autoantibodies recognized cryptic and native FAH epitopes in MHV-infected mice. Two homologous peptides of both FAH and the nucleocapsid were recognized by most antibodies [17].

3. Common human coronaviruses and multiple sclerosis

Seven types of coronavirus are known to infect humans (Table 1). The most common human coronaviruses circulating worldwide are OC43, HKU1, NL63, and 229E [18].

Multiple sclerosis is an immune-mediated demyelinating disease in which infectious pathogens could play a role in the pathogenesis of the disease. The possible involvement of human coronaviruses as an environmental trigger of multiple sclerosis (MS) is supported by several studies. Antibodies to coronaviruses OC43 and 229E were found in the cerebrospinal fluid of MS patients more frequently and in higher titers than that of matched controls [19]. Moreover, intrathecal antibody synthesis to OC43 and 229E coronaviruses has been found in 41% and 26% of MS patients, respectively [19]. Human coronavirus HCV-229E can replicate in cultures of various human neuronal and glial cell lines [20]. Human coronavirus 229E viral RNA has been detected in the brain tissue of MS patients [21]. Molecular mimicry has been proposed as a putative mechanism in the pathogenesis of MS. T-cell lines isolated from MS patients show cross-reactivity between myelin basic protein and viral antigens from the human respiratory coronavirus 229E [22].

4. SARS-CoV and autoimmunity

In winter 2002-2003, severe acute respiratory syndrome (SARS) emerged in China and subsequently spread throughout the world. SARS is caused by a novel species of coronavirus that has been named SARS-CoV. SARS-CoV infection is characterized by a severe and potentially fatal lung disease. The pathogenic mechanisms of SARS include direct viral cytopathic effects, the dysregulation of cytokines/chemokines, the innate immune response, and the immunogenetics of the host [23, 24]. Several studies have suggested that autoimmunity may also be involved in the pathogenesis of SARS. During the acute phase of the disease, IgM and IgG autoantibodies against cytoplasmic antigens of pneumocytes were detected in the sera of 36 Chinese SARS patients [23]. In another cohort of 22 SARS patients, autoantibodies against human epithelial cells (the A549 human pulmonary epithelial cell-line) and human endothelial cells (human umbilical endothelial cells (HUVEC) and primary human pulmonary endothelial cells (HPEC)) developed approximately one month after the onset of the disease [25]. Sera from SARS patients with high-levels of autoantibodies induced complement-dependent cytotoxicity against A549 cells and HPEC [25]. Lin et al. also showed that antibodies present in the sera of SARS patients reacted with A549 epithelial cells (type-2 pneumocytes) [26]. These autoantibodies were primilary of IgG isotype and were detectable 20 days after the onset of fever, the IgG present in the sera of SARS patients had a cytotoxic effect on A549 cells [26]. Indeed, there are cross-reactive epitopes on domain 2 of the SARS-

CoV spike protein (S2) with human lung epithelial cell proteins. Anti-SARS-CoV spike antibodies enhance the adherence of human peripheral blood mononuclear cells to A549 cells [26]. Thus, the autoimmune responses in SARS-CoV infection may contribute to the pathogenesis of the disease.

Other groups identified sequence homology between four pathogenic regions of the SARS-CoV spike protein and various human proteins [27]. A proteomic approach showed annexin A2 to be an autoantigen in A459 cell-membrane extracts recognized by the sera of SARS patients and annexin A2 on lung epithelial cells was recognized by antibodies against SARS-CoV S2 [28]. Furthermore, anti-annexin A2 antibodies recognized purified S2 protein by ELISA. The authors also observed the upregulation of epithelial cell-surface expression of annexin A2 by Il-6 and INF-γ released during the cytokine storm in SARS infection [28]. The human long interspersed nuclear element 1 (LINE1) endonuclease domain was identified as a putative target of SARS-associated autoantibodies and these antibodies were found in 40.9% of patients with SARS [29].

5. Can SARS CoV-2 trigger autoimmunity ?

In December 2019, the first cases of patients with severe atypical pneumonia of unknown origin were reported in Wuhan, Hubei province, China. Most of these patients were epidemiologically linked to a seafood market in Wuhan. Pneumonia was caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 (previously known as 2019 novel coronavirus, 2019-nCoV, by the World Health Organization (WHO)). This newly emerged pathogen was isolated and sequenced in China [30, 31]. The disease caused by SARS-CoV-2 infection was later designated Coronavirus disease 2019 (COVID-19) by the WHO. SARS-CoV-2 infection has rapidly spread throughout the world. On March 11, 2020, the WHO declared the COVID-19 coronavirus outbreak a pandemic.

SARS-CoV-2 is the seventh type of coronavirus to be identified that infects humans. It belongs to the β coronavirus genus and has been classified under the orthocoronavirinae subfamily. Clinical presentation of COVID-19 mimics that of SARS-CoV infection. SARS-CoV-2 shows phylogenetic similarity to SARS-CoV, with the two genomes sharing 79.6% sequence identity [31]. SARS-CoV-2 interacts directly with angiotensin-converting enzyme 2 (ACE2) to enter host cells, particularly alveolar epithelial cells. The cellular entry of SARS-

CoV-2 is initiated through an interaction between the transmembrane spike (S) glycoprotein and the ACE2 receptor on human cells [32]. Furthermore, it has been shown that ACE2 was the same cell entry receptor for SARS-CoV [31] and that there is structural and sequence identity between the SARS-CoV-2 and SARS-CoV S glycoproteins [32]. COVID-19 is typically characterized by fever and respiratory illness, leading to acute respiratory distress syndrome, with admission to the intensive care unit (ICU) for 5% of patients [33]. However, several observations have shown that COVID-19 also shows a wide clinical spectrum, which includes cardiac injury in 20% of cases [34], venous thromboembolism in 25% of cases [35], disseminated intravascular coagulation, neurological manifestations, or skin involvement. A cytokine storm can be associated with severe forms of the disease [36, 37]. A two-phase immune response is induced by SARS-CoV-2 infection [38]. First, a specific adaptative immune response leads to viral clearance in most cases. However, immune dysregulation can occur in a subgroup of patients and lead to inflammation-induced lung damage and systemic complications. SARS-CoV-2 infection may therefore be associated with not only an auto-inflammatory response but also the development of an autoimmune process. Given the striking similarity between SARS-CoV infection and COVID-19, it is possible that COVID-19 may trigger an autoimmune process through molecular mimicry or the exposure of autoantigens caused by cytokine-induced organ injury.

Several reports have highlighted the link between COVID-19 and the development of autoimmunity. Patients with severe SARS-CoV-2 infection show a high risk of thrombosis [39]. The presence of antiphospholipid antibodies (APL) (anticardiolipin IgA and anti-β2 glycoprotein I IgA and IgG antibodies) has been reported in three patients with COVID-19 and multiple cerebral infarctions [40]. APL are common during infection. Such APL can be pathogenic but they also transiently arise in the context of viral infection. Harzallah et al. reported the presence of lupus anticoagulant (LA) in almost half of 56 patients with COVID-19 [41]. However, in a letter to the editor, Connell at al. suggested that the LA results may be false positives, given the high C-reactive protein levels in patients with COVID-19 [42]. Endothelial cell infection and diffuse endothelial inflammation were observed in a series of patients with COVID-19 and endothelial-cell injury was associated with apoptosis [43]. Therefore, it is possible that epitopes of host proteins became abnormally expressed on the plasma membrane surface of apoptotic endothelial cells, leading to the generation of autoantibodies, such as APL.

Several cases of Guillain-Barré syndrome in patients with COVID-19 have been reported [44-48]. GBS is an acute polyradiculoneuropathy associated with an aberrant autoimmune response and is generally preceded by a viral or bacterial infection. Although the pathogenic mechanisms need to be established, we cannot rule out molecular mimicry between viral epitopes and nerve antigens in the peripheral nerves, as has been suggested as one of the possible mechanisms for Zika virus-associated GBS [49]. However, no production of antibodies against specific gangliosides has been reported in patients with COVID-19 and GBS. Miller Fisher syndrome (MFS), a variant of GBS, is characterized by a triad of ataxia, areflexia and ophtalmoplegia. Several publications reported cases of MFS associated with COVID-19 infection. Only one patient was positive for anti-ganglioside GD1b IgG antibodies [50].

Other autoimmune disorders associated with COVID-19 include Immune Thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA). COVID-19 has been identified as a causal factor of ITP in a 65-year-old woman with HTA and autoimmune hypothyroidism [51]. Other authors described the first case series of 3 patients with ITP associated with COVID-19 [52]. Lazarian et al. reported seven cases of warm and cold AIHA associated with COVID-19 [53]. However, an indolent B cell malignancy was present in four of them. Furthermore, another case of AIHA during COVID-19 was reported in a 46-year old female with a medical history of congenital thrombocytopenia [54]. Several other hematologic disorders have been associated with COVID-19 such as cold agglutinin syndrome, Evans syndrome or autoimmune thrombotic thrombocytopenic purpura [55-57]. The structural similarity between an erythrocyte membrane protein named ANK-1 and the viral protein spike led Angileri et al. to postulate that molecular mimicry could contribute to the pathogenesis of COVID-19-associated AIHA [58].

In a single-center, retrospective study from an ICU of China'hospital (province of Hubei), the authors described clinical and autoimmune characteristics in 21 severe or critical cases of patients infected with SARS-CoV-2. They detected the presence of anti-52 kD SSA/Ro antibodies, anti-60 kD SSA/Ro antibodies, and antinuclear antibodies in 20%, 25%, and 50% of patients, respectively [59]. More recently, a study from the ICU of Evangelismos Hospital, Athens (Greece), showed the presence of several autoantibodies related to systemic autoimmune rheumatic diseases in almost 70% of severely ill patients with COVID-19 [60]. The major autoimmune findings for both SARS-CoV and SARS-CoV-2 are reported in Table 2.

As already described for SARS, the spike surface glycoprotein could play a role in COVID-19-associated immunopathology. Kanduc and Shoenfeld suggested that because the peptide sharing between spike glycoprotein from SARS-CoV-2 and human surfactant-related proteins, the immune response following SARS-CoV-2 infection might contribute to the SARS-CoV-2-associated lung diseases [61]. However, SARS-CoV-2 includes numerous other proteins that could represent an antigen source for the development of autoimmunity. Lyons-Weiler performed a bioinformatics analysis of the homology between highly immunogenic SARS-CoV-2 epitopes and human proteins. Among the SARS-CoV-2 proteins, those with the largest number of immunogenic peptides were the S protein and the non-structural protein NS3 [62]. Vojdani and Kharrazian reported a potential cross-reactivity between SARS-CoV-2 proteins (spike and nuclear proteins) and human tissue antigens [63]. Lucchese and Flöel reported that the SARS-CoV-2 proteome share three sequences of six aminoacids (GSQASS, LNEVAK, SAAEAS) with three human proteins (DAB1, AIFM, SURF1) related to the respiratory pacemaker in the brainstem. The authors postulated that molecular mimetism between neuronal and viral proteins might contribute to autoimmune mediated respiratory failure [64]. Angileri et al. also suggested that some features of COVID-19 such as anosmia, leukopenia and multi-organ damage could be the consequence of similarities between SARS-CoV-2 proteins (ORF7b, ORF1ab, nucleocapsid phosphoprotein) and the following human proteins: OR7D4, PARP9 and SLC12A6, respectively [65]. More recently, Megremis et al. identified three immunogenic linear epitopes with high sequence identity to SARS-CoV-2 protein in patients with autoimmune dermatomyositis [66]. On the basis of these reports, autoimmunity may be, at least partially, involved in the pathogenesis of COVID-19 in genetically predisposed individuals. Further studies will be needed to better characterize the possible link between COVID-19 and the development of autoimmunity, particularly in patients with severe interstitial pneumonia.

6. Conclusion

Coronaviruses represent a large group of virus affecting many species of animals and humans, causing acute and chronic diseases. From animal models to human diseases such as SARS and COVID-19, several studies have highlighted the possible role for autoimmunity through molecular mimicry in coronavirus pathogenesis. The wide spectrum of autoimmune-like manifestations in SARS-CoV-2-infected patients suggests that COVID-19 represents the better example of coronavirus-induced autoimmunity. However, it would be useful to better

characterize the role of autoimmunity in pathogenesis COVID-19, particularly in patients with severe forms of disease.

The authors have no conflicts to declare

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Table 1

Human coronavirus types
Common human coronaviruses
229E (alpha coronavirus)
NL63 (alpha coronavirus)
OC43 (beta coronavirus)
HKU1 (beta coronavirus)
Other human coronaviruses
MERS-CoV (the beta coronavirus reponsible for Middle East Respiratory Syndrome, MERS)
SARS-CoV (the beta coronavirus reponsible for severe acute respiratory syndrome, SARS)
SARS-CoV-2 (the novel beta coronavirus that causes Coronavirus disease 2019, COVID-19)

Table 2

Major autoantibodies reported in SARS-CoV and SARS-CoV-2-infected patients

SARS-CoV	SARS-CoV-2
Anti-lung epithelial cell	Antiphospholipid antibodies
Anti-endothelial cell	- anti-cardiolipin antibodies
Anti-annexin A2	- anti-β2 glycoprotein I antibodies
Anti-endonuclease of the human LINE1	- lupus anticoagulant
	Anti-nuclear antibodies
	p-ANCA and c-ANCA
	Anti-CCP antibodies
	Anti-ganglioside GD1b antibodies

CCP, cyclic citrullinated peptide ; ANCA, anti-neutrophil cytoplasmic antibody