



# Dysregulation of immunity in COVID-19 and SLE

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## Abstract

The immune response plays a crucial role in preventing diseases, such as infections. There are two types of immune responses, specific and innate immunity, each of which consists of two components: cellular immunity and humoral immunity. Dysfunction in any immune system component increases the risk of developing certain diseases. Systemic lupus erythematosus (SLE), an autoimmune disease in the human body, develops an immune response against its own components. In these patients, due to underlying immune system disorders and receipt of immunosuppressive drugs, the susceptibility to infections is higher than in the general population and is the single largest cause of mortality in this group. COVID-19 infection, which first appeared in late 2019, has caused several concerns in patients with SLE. However, there is no strong proof of additional risk of developing COVID-19 in patients with SLE, and in some cases, studies have shown less severity of the disease in these individuals. This review paper discusses the immune disorders in SLE and COVID-19.

**Keywords** Systemic lupus erythematosus (SLE) · COVID-19 · Autoimmunity · Immune response

## Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the Coronaviridae family of viruses, which is responsible for the pneumonia outbreak in late December 2019, later officially announced as a pandemic (Nokhostin et al. 2020; Cucinotta and Vanelli 2020). This virus can cause severe acute respiratory syndrome (SARS), a potentially life-threatening condition (Thienemann et al. 2020). Other manifestations of the disease include altered white blood cell (WBC) counts, impaired liver function tests (LFT), and increased inflammatory cytokines (Lei

et al. 2020). Cytokines are one of the main components of the immune system, and their increased production causes impaired immune response called cytokine storm syndrome (CSS), seen in severe cases (Fajgenbaum et al. 2020). It has been shown that cytokine dysregulation can lead to more serious conditions such as autoimmune diseases (ADs), including systemic lupus erythematosus (SLE), in COVID-19 patients (Kyttaris 2019; Najafi et al. 2020). One suggested pathophysiology includes excessive cytokine production that can lead to a loss of tolerance to self-antigens (Franceschi et al. 2018; Hemminki et al. 2020; Patra et al. 2020).

ADs are caused by immune system response against self-antigens, which causes inflammation and damage to various tissues and organs of the body based on the nature of the disease (Bogoch et al. 2020). SLE is an AD that can involve the musculoskeletal, hematologic, integumentary, renal, and central nervous (CNS) systems (Kuhn et al. 2015). There is a close relationship between infections and mortality in SLE patients (Iliopoulos and Tsokos 1996). Approximately one-third of patients with SLE die due to infections, specifically respiratory infections (Rúa-Figueroa et al. 2017; Thomas et al. 2014). Multiple mechanisms expose SLE patients to infections, including alterations in immune responses, therapy with immunosuppressive drugs, and concomitant morbidities (Hou et al. 2018; Cohn 1991).

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COVID-19 and ADs have many common disastrous outcomes, including kidney damage, which is accompanied by more severe clinical conditions in both diseases. Kidney damage in SLE patients is due to increased levels of interleukin-23 (IL-23), interferon gamma (IFN- $\gamma$ ), and IL-17, which are produced by T helper 17 (Th17) cells (Zickert et al. 2015; Oke et al. 2017). Studies have revealed that the level of serum inflammatory cytokines in COVID-19 patients with better clinical conditions is lower than that in patients admitted to the intensive care unit (ICU) (Huang et al. 2020a; Xu et al. 2020a). This suggests that complications in COVID-19 patients may be due to an increase in the rate of cytokine production. On the other hand, similarities in COVID-19 and SLE pathophysiology may provide insight into new COVID-19 therapeutic approaches based on therapies currently used in SLE patients, which aim to suppress immune system over-activation and control cytokine output (Valencia et al. 2019). Therefore, this paper discusses the immune responses and immune system dysregulation in COVID-19 and the AD SLE.

### The incidence of COVID-19 in autoimmune diseases

Despite the enhanced risk of COVID-19 in ADs, little evidence is available on the subject (Favalli et al. 2020), although some studies have proposed the possibility of an increased risk of developing COVID-19 in these patients (Cohn 1991; Sawalha et al. 2020; Gianfrancesco et al. 2020a; Horisberger et al. 2020). In a recent study by Mathian et al., among 17 SLE patients with COVID-19, 14 were admitted to the hospital, among which only two died due to severe respiratory infection (Mathian et al. 2019). In another study by Monti et al., among 320 patients treated with different antirheumatic agents, only four patients had confirmed diagnosis of COVID-19 (Monti et al. 2020). The data from the COVID-19 Global Rheumatology Alliance global registry as of March 1, 2022, showed that 1794 SLE patients had been diagnosed with COVID-19 (The Global Rheumatology Community's Response to the Worldwide COVID-19 Pandemic 2022). A recent study considered the outcome of rheumatic disease patients who were under different therapies (Gianfrancesco et al. 2020b). Patients receiving prednisone at a dose greater than 10 mg/day were at higher risk for severe disease and ICU hospitalization. On the other hand, patients using anti-tumor necrosis factor alpha (TNF- $\alpha$ ) agents had a decreased risk of admission. There was no change in the outcome of individuals treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or hydroxychloroquine (HCQ) (Gianfrancesco et al. 2020b).

It is now well established that increased circulating levels of angiotensin-converting enzyme 2 (ACE2) and

immunosuppressive therapies are potential mechanisms in favor of increased risk of COVID-19 in SLE patients (Sawalha et al. 2020). Paradoxically, the other aspect of immunosuppressant use in SLE patients is the decreased chance of severe lung injury in infected patients due to the anti-inflammatory effect of these agents (Horisberger et al. 2020). The ACE2 gene is located on the X chromosome, and DNA methylation plays a critical role in its expression (Jin et al. 2011). SLE patients have increased levels of ACE2 in their bloodstream resulting from decreased methylation of the ACE2 gene (Sawalha et al. 2020). Additionally, cell entry of COVID-19 viruses, the essential step in virus pathogenesis, is mediated by ACE2 (Hoffmann et al. 2020). Therefore, it is possible that the elevated levels of ACE2 in SLE patients, along with the increased levels of apolipoprotein E (ApoE) and TNF- $\alpha$ , might lead to a higher risk of COVID-19 viremia in these patients (Sawalha et al. 2020; Monti and Montecucco 2020).

Distinguishing SLE complications such as acute lupus pneumonitis from COVID-19 is not a straightforward diagnosis due to their clinical and laboratory similarities with severe cases of COVID-19 (Soloway et al. 2021; Kichloo et al. 2020). Soloway et al. reported a case of an SLE patient with acute lupus pneumonitis which masked her COVID-19 infection due to the consumption of a high dose of an immunosuppressive agent, including steroids, causing readmission for coronavirus pneumonitis (Soloway et al. 2021). In another study by Kichloo et al., a 22-year-old SLE patient with acute lupus pneumonitis, superinfected with COVID-19, was successfully managed with intravenous administration of a high dose of corticosteroids (Kichloo et al. 2020). These findings highlight the importance of considering COVID-19 in all SLE patients on high-dose steroid therapy who are admitted to hospitals, even with atypical findings for COVID-19.

In contrast to studies suggesting an increased likelihood of COVID-19 in SLE, some studies have raised the possibility of decreased COVID-19 risk in these patients. One issue considered by these studies is the drugs used in SLE treatment, which were initially thought to exacerbate or increase the risk of COVID-19 infection. However, over time, studies have revealed that not only are some of these drugs not harmful, but they can also be used to treat COVID-19 (Kokkotis et al. 2022; Brito et al. 2021; Guo et al. 2022; Wagner et al. 2021). It has been shown that an increased serum level of ACE2 is related to elevated TNF- $\alpha$  production (Channappanavar et al. 2016), the serum level of which is increased in COVID-19 patients (Huang et al. 2020a; Chen et al. 2020b). Thus it is not surprising that anti-TNF- $\alpha$  drugs which are used to treat SLE patients might have beneficial effects in the treatment of COVID-19 patients, as some studies have reported promising results (Kokkotis et al. 2022; Brito et al. 2021; Guo et al. 2022; Haga et al. 2008; Feldmann et al. 2020).

## The incidence of autoimmune diseases in COVID-19

Different types of immune dysregulation are implicated in the main pathogenesis of both ADs and COVID-19, causing disturbed self-tolerance and autoimmune responses (Jakiela et al. 2018). As an example, autoantibodies which are the hallmark of ADs are also seen in COVID-19 patients (Huang et al. 2020b; Bastard et al. 2020). Some studies have also reported the incidence of new cases of ADs, including Guillain–Barré syndrome (GBS) (Alberti et al. 2020; Toscano et al. 2020; Virani et al. 2020; Coen et al. 2020; Scheidl et al. 2020; Caamaño and Beato 2020; Arnaud et al. 2020; Gutiérrez-Ortiz et al. 2020; Ottaviani et al. 2020; Dinkin et al. 2020), Kawasaki disease (KD) (Nathan et al. 2020; Toubiana et al. 2020; Jones et al. 2020; Riphagen et al. 2020; Verdoni et al. 2020; Rivera-Figueroa et al. 2020), SLE (Zamani et al. 2021), hemolytic anemia (Lazarian et al. 2020; Jacobs and Eichbaum 2021; AbouYabis and Bell 2021), and immune thrombocytopenic purpura (ITP) (Zulfiqar et al. 2020; Kuter 2021) after COVID-19 infection.

## Autoimmunity in COVID-19

ADs result from loss of tolerance to self-antigens and aberrant activation of the immune system. Multiple factors, including environmental, genetic, and hormonal factors, contribute to the pathogenesis of these diseases (Wang et al. 2015; Moody et al. 2021). COVID-19 can mimic autoimmune and auto-inflammatory conditions by breaking the immunological tolerance, which is mediated by different mechanisms including bystander activation, molecular mimicry, and epitope spreading (Smatti et al. 2019; Rojas et al. 2018; Pacheco et al. 2019). Accordingly, it has been proposed that the possible mechanism of central respiratory depression in patients with COVID-19 is the similarity of the SARS-CoV-2 proteome to three human proteins, AIFM, DAB1, and SURF1, which are located in the respiratory pacemakers of the brainstem, also classified as pre-Bötzinger complex (Lucchese and Flöel 2020). Similarly, Kanduc et al. reported that the SARS-CoV-2 proteome contains several pentapeptides similar to pulmonary surfactants, revealing a possible mechanism behind the pulmonary damage in COVID-19 (Kanduc and Shoenfeld 2020). Moreover, after the clearance of the virus in pneumocytes, the inflammatory processes continue in the lung as a result of epitope cross-reaction between lung tissue and the SARS-CoV-2 virus (Huang et al. 2020b). Recent studies have reported strong

cross-reactions between the spike protein of SARS-CoV-2 and various human tissue proteins such as transglutaminase 2, transglutaminase 3, ENA, thyroid peroxidase, mitochondria, myelin basic protein,  $\alpha$ -myosin, collagen, claudin-5 + 6, and S100B, resulting in autoantibody production (Rodríguez et al. 2020; Vojdani and Kharratian 2020). The other issue suggesting a similar mechanism behind immunological responses in SLE and COVID-19 is the same immunomodulatory agents used in the treatment of both SLE and COVID-19 patients (Luo et al. 2020; Ahn et al. 2019; Cantini et al. 2020).

## The innate immune response in COVID-19 and SLE

The innate immune system serves as the primary barrier against viruses and uses pattern recognition receptors (PRRs) to induce immune responses (Diamond and Kanneganti 2022). This immune system consists of different immune cells, including neutrophils, macrophages, dendritic cells, monocytes, and especially innate lymphoid cells (ILCs) such as natural killer (NK) cells. PRRs recognize the pathogen-associated molecular patterns (PAMPs) which exist in all pathogens and the damage-associated molecular patterns (DAMPs), and are related to cell damage (Kanneganti 2020). The main PRR families consist of toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors, and absent in melanoma 2 (AIM2)-like receptors (Kanneganti 2020). Several types of PRRs, including TLRs, RLRs, and NLRs, are involved in the SARS-CoV-2 immune response (Diamond and Kanneganti 2022).

## NK cells in COVID-19 and SLE

NK cells are one of the key elements of the innate immune system exhibiting cytotoxic activity, and play a critical role in the early response to viruses and proper coordination between innate and adaptive immune systems (Leem et al. 2021; Schuster et al. 2016). NK cell function is controlled by many activating and inhibiting receptors. Cell activation causes cytotoxicity and production of inflammatory cytokines, known as cytotoxic and inflammatory phenotypes, respectively (Schuster et al. 2016; Vivier et al. 2008; Lanier 2008; Kärre 2002). The inactivation of NK cells rests upon the "self" signals via the major histocompatibility complex class I (MHC-I) molecules expressed on all healthy cells, which leads to "self-tolerance" (Lanier 2008; Kärre 2002). The inhibitory receptors that are expressed on NK cells and are specific for MHC-I include lectin-like CD94/NKG2A

heterodimers and the killer cell immunoglobulin-like receptors (KIRs) (KLRG1 and TIGIT) (Lanier 2008; Long et al. 2013; Eeden et al. 2020). NK cells are also essential for modulating other immune components, especially T cells, and act in both direct and indirect (using antigen-presenting cells [APC] such as dendritic cells [DCs]) ways (Schuster et al. 2016; Lanier 2008). The direct interaction is mediated by cytokines, including IFN- $\gamma$  as the activator agent and IL-10 as the inhibitory cytokine (Schuster et al. 2016; Lanier 2008). The cytotoxic elimination of activated T cells is the other direct way of regulating T cell function by NK cells. This is based on the increased activating ligands (NKG2D) and diminished inhibitory ligands (MHC-I) on activated T cells, making it possible for them to be recognized by NK cells (Lanier 2008; Kärre 2002). In addition, the decreased number of T cells, specifically T follicular helper (Tfh) cells, indirectly inhibits the B-cell-mediated immunity by NK cells (Zhang et al. 2013).

The total quantity of NK cells is reduced in SLE, and the existing NK cells show less cytotoxicity than normal NK cells (Park et al. 2009; Schleinitz et al. 2010). Segerberg et al. reported that there are several circulating autoantibodies against the multiple KIR receptors and the human leukocyte antigen (HLA) class I-binding receptors (NKG2A, NKG2C) in SLE patients, which disturb the self- and non-self-recognition by NK cells (Hagberg et al. 2015; Segerberg et al. 2019). Moreover, B- and T-cell-mediated altered immune response in ADs is thought to be the primary pathophysiology of these diseases. In terms of the altered adaptive immune response, these cells are impacted by the stimulation of NK cells and self-tolerance mechanisms (Giancchetti et al. 2018). Similarly, researchers have demonstrated that COVID-19 patients have a decreased total number of NK and CD8+ T cells, which show a functionally exhausted phenotype (Zheng et al. 2020; Li et al. 2020; Wang et al. 2020). This is determined based on the enhanced expression of NKG2A, LAG3, PDCD1, and HAVCR2 as NK cell exhaustion indicators, and PD-1 and Tim-3 as T cell inhibitory factors (Zheng et al. 2020; Wilk et al. 2020). Increased expression of NKG2A in NK cells is accompanied by reduced expression of TNF- $\alpha$ , IFN- $\gamma$ , and IL-2 and down-regulation of granzyme B (Ndhlovu et al. 2012; Gleason et al. 2012). Tim-3 has a dual effect on NK cells. On the one hand, it increases the expression of IFN- $\gamma$  in these cells, and on the other hand, its enhanced expression is accompanied by a significant drop in NK cell cytotoxicity (Ndhlovu et al. 2012; Gleason et al. 2012). Studies have suggested that lower expression of NKG2C may worsen COVID-19 outcome (Vietzen et al. 2020).

There are two types of conventional NK cells based on their surface molecules, including the CD56<sup>DIM</sup>/CD16<sup>POS</sup>/CD56<sup>BRIGHT</sup>/CD16<sup>NEG</sup> subsets. The first type has a cytotoxic phenotype and is predominantly found in peripheral

blood (Vivier et al. 2008; Moretta et al. 2001), whereas the second type comprises cytokine-producing NK cells, usually located in the secondary lymphoid tissues and activated following interaction with IL-12, IL-15, and IL-18 cytokines (Vivier et al. 2008; Long et al. 2013; Moretta et al. 2001; Cooper et al. 2001). CD56<sup>DIM</sup>/CD16<sup>NEG</sup> (uCD56<sup>DIM</sup>) is the other member of the NK cell population, which is found in small numbers in healthy individuals and can be expanded in several disorders (Amand et al. 2017; Fan et al. 2008). A recent study demonstrated that the unconventional subset of NK cells (CD56<sup>DIM</sup>/CD16<sup>NEG</sup>) is increased in patients with COVID-19, regardless of the disease severity, and is associated with reduced NK cell cytotoxicity. Recovery to normal NK cell population was faster in patients with mild symptoms (Leem et al. 2021). In another study, Wilk et al. reported that the expression of multiple genes related to NK cell function and maturity is decreased in COVID-19 patients (Wilk et al. 2020), among which FCGR3A and FGF2 are specifically related to CD56<sup>DIM</sup> NK cells (Crinier et al. 2018). In a study by Leng et al., patients with COVID-19 were found to have elevated expression of CXCR3+, which is a marker of NK cells and is more common among the CD56<sup>BRIGHT</sup> NK cell subpopulation (Leng et al. 2020). Altogether, these findings suggest a shift toward more inflammatory NK cell traits in COVID-19 infection (Osman et al. 2020). Additionally, the balance between the CD56<sup>DIM</sup> and CD56<sup>BRIGHT</sup> NK cell population is disturbed in SLE patients, where the proportion of the CD56<sup>DIM</sup> subpopulation is decreased (Henriques et al. 2013; Spada et al. 2015; Liu et al. 2021). Interestingly, the CD56<sup>DIM</sup> NK cells present in SLE patients tend to produce elevated levels of IFN- $\gamma$ , and the expression of activating receptors, including NKp44, NKp46, and CD69, is increased in these cells (Liu et al. 2021).

## Cytokine storm

Cytokine storm is the excessive production of cytokines with inflammatory activity, present in many infectious and noninfectious conditions, resulting from inflammation (Tisoncik et al. 2012). It is believed that this phenomenon is a crucial component in COVID-19 pathogenesis and is related to its severe manifestations, such as acute respiratory distress syndrome (ARDS) (Huang et al. 2020a; Jiang et al. 2022; Hu et al. 2021). Indeed, many studies have demonstrated enhanced levels of cytokines of an inflammatory nature in COVID-19 patients, including IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-6, IL-10, granulocyte macrophage-colony stimulating factor (GM-CSF), inducible protein 10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1) (Huang et al. 2020a; Ruan et al. 2020; Valle et al. 2020; Zhu et al. 2020; Chen et al. 2020a).

Several mechanisms have been suggested as the principal mechanisms underlying cytokine storm progression in COVID-19, all common in the inadequate immune response against the virus (Jiang et al. 2022; Frisoni et al. 2021; Maiese et al. 2020; Blanco-Melo et al. 2020; Bastard et al. 2021; Wang et al. 2021; Lv et al. 2021; Domingo et al. 2020; Bourgonje et al. 2020; Zanza et al. 2021). Blanco-Melo et al. demonstrated that antiviral IFN production is impaired in COVID-19 patients (Blanco-Melo et al. 2020). Such impaired innate immune response makes replication much easier for the virus. Likewise, Lv and colleagues noted that the SARS-CoV-2 virus could survive in the M1 subpopulation of alveolar macrophages, facilitating the spread of infection throughout the lungs (Lv et al. 2021). Anti-type I IFN antibodies, along with the autoantibodies against other immune proteins, are another potential reason for decreased IFN response in SARS-CoV-2-infected patients (Bastard et al. 2021; Wang et al. 2021). Many studies have also shown increased levels of chemokines and cytokines after the SARS-CoV-2 virus enters the human body (Jiang et al. 2022; Blanco-Melo et al. 2020; Osman et al. 2020). As an example, increased function of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome during COVID-19 results in increased production of IL-18 and IL-1 $\beta$  (Hadjadj et al. 2020; Schmidt and Lenz 2012; Zheng et al. 2014). After successful reproduction of SARS-CoV-2 in an environment lacking antiviral IFNs, accompanied by the increased levels of chemokines and cytokines, the exaggerated immune reaction to the virus causes a cytokine storm in the second stage of COVID-19 infection (Chowdhury et al. 2020). Based on the anti-inflammatory consequences of the ACE2 receptor (Sodhi et al. 2019; Nabah et al. 2004), Diamond et al. hypothesized a possible role of the renin–angiotensin–aldosterone system (RAAS) in the pathogenesis of increased cytokine storm in COVID-19. They also suggested that the decreased level of ACE2 receptor is responsible for the increased thrombo-inflammatory state in COVID-19 (Diamond 2020).

The role of cytokine storm in the pathogenesis of SLE is much more limited than in COVID-19. However, similar to COVID-19, there is supporting proof that shows an increased rate of cytokines such as TNF- $\alpha$ , B-lymphocyte stimulator (BLyS), type I IFNs, IL-6, IL-17, and IL-18 in SLE (Yap and Lai 2013). Furthermore, the use of cytokine inhibitory agents has been suggested as a therapeutic strategy in severe SLE patients and intriguingly, some studies have announced promising results (Huang et al. 2020a; Clark et al. 2013). In a recent study by Xu et al. on pristane-induced murine models of lupus, IL-38 levels were demonstrated to be increased in these mice. However, unexpectedly, they experienced a reduction in lupus development after using IL-38 suggesting the possible anti-inflammatory role of this cytokine in SLE (Xu et al. 2020b).

## IFN responses in COVID-19 and SLE

The prominent role of type I interferon response in the pathogenesis of both rheumatoid and viral infections is undeniable (Rönnblom and Pascual 2008; Muskardin and Niewold 2018; Tariq et al. 2021; Vardhana and Wolchok 2020). However, many studies have reported decreased production of type I IFNs in COVID-19 (Blanco-Melo et al. 2020). Moreover, a recent study demonstrated that neutralizing autoantibodies against type I IFNs are seen in a minimum of 10% of patients with severe COVID-19 (Bastard et al. 2020). Accordingly, it can be theorized that high titers of type I IFN in patients with SLE may prevent the incidence of COVID-19 in these patients due to the more effective viral clearance.

Studies have reported the incidence of new cases of SLE after recombinant human IFN- $\alpha$  administration in patients with hematologic malignancies. These patients experience an improvement in their symptoms after the drug is ceased (Rönnblom et al. 1990; Niewold and Swedler 2005). Moreover, healthy relatives of SLE patients have been found to have high levels of type I IFN in their serum, suggesting a role of type I IFN genetic alterations in the immunopathology of SLE (Niewold et al. 2007; Kariuki et al. 2010). Furthermore, many SLE-associated disparities in the genes of the type I IFN pathway are accompanied by enhanced activity of the IFN-I pathway (Niewold 2011; Niewold et al. 2010; Bronson et al. 2012; Ghodke-Puranik and Niewold 2013). In addition, in some patients with SLE, elevated activity of type I IFN was reported during the year before they were diagnosed (Munroe et al. 2016).

## Adaptive immunity (cell-mediated response)

As mentioned above, many studies have reported decreased number and exhausted phenotype (based on the excessive expression of PD-1 and Tim-3 as T cell exhaustion markers) of CD8+ T cells in COVID-19 patients (Zheng et al. 2020; Li et al. 2020; Wang et al. 2020). In contrast, based on elevated HLA-DR and CD38 as T cell activator markers, many other studies have demonstrated higher levels of T cell activation (Xu et al. 2020a; Diao et al. 2019; Wang et al. 2020; Qin et al. 2020). Furthermore, an elevated neutrophil-to-lymphocyte ratio (NLR) is found in COVID-19, indicating the inflammatory state of this disease (Qin et al. 2020). Taken together, these findings suggest significant changes in cell-based immunity against COVID-19, which are discussed below in detail.

## T cells in COVID-19 and SLE

Although the main characteristic of SLE is the excessive production of autoantibodies by B cell lymphocytes, the role of T lymphocytes cannot be ignored. (Katsuyama et al. 2018; Mak and Kow 2014). Several functional changes in T cells are seen during SLE. For example, the expression of CD3 $\zeta$  (CD247), a T cell surface protein, is decreased in SLE, leading to a shift in intracellular signaling to the Syk pathway (Katsuyama et al. 2018). The activation of the Syk pathway gives rise to vigorous calcium flux in T cells, leading to hyper-inflammation (Katsuyama et al. 2018). This process results in the upregulation of CD40 ligand (CD40L) in patients with active SLE.

CD40L is a co-stimulatory protein on T cells which helps them engage with other cells with CD40 molecules, such as B cells leading to activation of B cells (Mak and Kow 2014). As CD40 is present on many other cell types, including myocytes, platelets, and endothelial cells, which are robustly involved in positive inflammatory feedback, CD40L may cause several undesired side effects leading to inflammation (Goshua et al. 2020; Karnell et al. 2019).

The role of T lymphocytes in the occurrence of COVID-19 is much more of a double-edged blade. Although the protective role of T cells against the spike protein of the COVID-19 virus is established, the same cells could have uncontrolled proinflammatory responses (Toor et al. 2021). It has been shown that COVID-19 patients admitted to the ICU have higher levels of CD40L on their platelets and T lymphocytes, resulting in excessive inflammation, poor prognosis, and a hypercoagulable state (Goshua et al. 2020). This is concerning due to the hypercoagulable state of patients with active SLE that is already well established (Misra et al. 2020; Bowles et al. 2020).

## Th17 cells in COVID-19 and SLE

Th17 cells are a member of CD4+ T lymphocytes that are capable of producing proinflammatory cytokines, including IL-17A, IL-17F, and IL-22, and are specified by the expression of the RAR-related orphan receptor gamma (ROR $\gamma$ T) transcription factor (Yang et al. 2009; Littman and Rudensky 2010). This is why these cells are also known as an inflammatory Th subset (Yasuda et al. 2019). It has been shown that patients with SLE have increased numbers of Th17 cells and IL-17 cytokines in their bloodstream, and the severity of this immunological disorder is negatively associated with their clinical outcome (Shan et al. 2020). IL-17 is capable of inducing autoantibody synthesis in patients with lupus nephritis (LN) (Lee et al.

2019). Several studies have demonstrated increased levels of the mammalian target of rapamycin complex (mTORC) in SLE (Katsuyama et al. 2018). In a study by Singh and colleagues, development of a fulminant SLE was reported in a patient with a downregulated level of a negative regulator of mTORC1, which led to the patient's death (Singh et al. 2013). mTORC is a nutrient sensor and is involved in the cell cycle management. mTOR has a primary role in the activation and polarization of naïve T cells (Katsuyama et al. 2018; Terrazzano et al. 2020; Zeng et al. 2013 Jul). Furthermore, a study demonstrated that SLE patients with LN have high rates of circulating Th17 cells and decreased Treg/Th17 ratio; however, no association with disease activity was found (Jakiela et al. 2018).

Another study by Abdel Galil and colleagues reported a direct association between IL-17 serum levels and proteinuria or anti-double-stranded DNA antibodies (anti-dsDNA ab) in patients with LN (Abdel Galil et al. 2015). As seen in SLE, many studies have shown increased activity of Th17 cells and elevated levels of IL-17 in COVID-19 (Biasi et al. 2020; Gadi et al. 2020). Another study established that the increased level of IL-17A is accompanied by increased damage to the lung tissue, leading to more severe disease in COVID-19 (Parackova et al. 2021). Furthermore, a high ratio of Th17 to Treg cells is correlated with poor prognosis in COVID-19 (Sadeghi et al. 2021).

## Lymphopenia in SLE and COVID-19

Lymphopenia, with a predominant decrease in T lymphocytes, is an expected finding in SLE that has recently been detected in COVID-19 and used as a prognostic factor in these patients (Martin et al. 2017; Frater et al. 2020). Five main processes were found to be involved in the incidence of lymphopenia in SLE, including (1) the presence of immunoglobulin M (IgM) and/or IgG lymphocytotoxic antibodies against T-cell-rich antigens including CD4, CD45, MHC-II, glycopospholipids, and ribosomal P protein (Martin et al. 2017), (2) a decrease in the intracellular antioxidant glutathione, which causes increased apoptosis in T cells (Shah et al. 2012), (3) enhanced expression of Fas on naïve and memory T cells, which causes apoptosis (Bijl et al. 2001; Papo et al. 1998), (4) decreased expression of complement regulatory proteins, specifically CD55, CD59, and CD46, which expose T cells to complement-mediated cytotoxicity (Alegretti et al. 2012), and (5) decreased lymphopoiesis and increased T cell sequestration in secondary lymphoid organs and inflammatory sites due to the reduced number of CD34+ hematopoietic progenitors and enhanced level of IFN- $\gamma$  which is associated with limited self-renewal of hematopoietic stem cells. This process is induced by transcription factor PU.1 hyper-expression (Spihlman et al.

2020). It has evident that SLE patients have elevated levels of IFN- $\gamma$  (Oke et al. 2017; Munroe et al. 2016; Bengtsson et al. 2000; Rana et al. 2012).

Similar to the mechanisms implicated in SLE pathogenesis, multiple mechanisms are hypothesized to be involved in the development of lymphopenia in COVID-19. The first possible mechanism is the excessive production of inflammatory cytokines, which causes increased apoptosis in T cells. Studies have demonstrated an increased rate of T cell apoptosis mediated by type I IFN and IFN- $\gamma$ , which are abundant in COVID-19 (Channappanavar et al. 2016; Perl et al. 2004). Epithelial cells infected with SARS-CoV-2 release TNF- $\alpha$ , which induces T cell apoptosis (Wang et al. 2018). Additional studies have proposed the role of other proinflammatory cytokines, including IFN- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, and IL-33 (Fathi and Rezaei 2020; Okoye et al. 2017; Huang and Pranata 2020; Lin et al. 2020). In justification of high T cell apoptosis in COVID-19, one study demonstrated that the increased expression of the TP53 gene is a key factor in induction of apoptosis (Xiong et al. 2020). During COVID-19, T cell sequestration in the lungs, gastrointestinal tract, and lymphoid tissues is also involved in lymphopenia. A positive correlation is seen between lymphopenia and poor prognosis in patients with COVID-19 (Frater et al. 2020).

## Adaptive immunity (humeral response)

### Antibody role in COVID-19 and SLE

Anti-dsDNA autoantibodies are diagnostic hallmarks of SLE which lead to the deposition of the immune complexes throughout the body, specifically joints, blood vessels, and the renal system (Spihlman et al. 2020; Rekvig 2015). Different theories exist in terms of autoantibody production in SLE. Some studies have suggested the possible role of viruses, especially polyomavirus group viruses, while others have proposed the possible role of DNA-binding proteins through molecular mimicry (Rekvig 2015; Ahsan and Shah 2006). Moreover, increased apoptosis or insufficient clearance of apoptotic cells results in autoantigen-antibody complex production, which in turn stimulates IFN- $\alpha$  expression, leading to immune reactivity (Pan et al. 2020). Interestingly, a recent study reported elevated levels of autoantibodies such as antinuclear antibody (ANA) in about 34.5% of COVID-19 patients with severe infection (Vlachoyiannopoulos et al. 2020). Many studies have also shown positive anti-phospholipid antibodies (APL) consisting of anti-cardiolipin (aCL), lupus anticoagulant (LA), and anti- $\beta$ 2 glycoprotein ( $\beta$ 2GPI) in COVID-19 infection, which may be accompanied by thrombotic events (Bowles et al. 2020; Zhang et al. 2020;

Harzallah et al. 2020; Helms et al. 2020; Amin 2008; Zuo et al. 2020). However, a study reported no enhanced risk of increased major thromboembolic accidents in COVID-19 patients (Borghetti et al. 2020). Surprisingly, another study showed that the APL antibodies in COVID-19 are not the same as those in SLE (Borghetti et al. 2020).

IgM, IgG, and mucosal and systemic IgA are the most common types of SARS-CoV-2-specific antibodies in COVID-19 patients. Many of these antibodies are secreted in reaction to the S and N proteins of the virus (Guo et al. 2020; Lou et al. 2020; Whitman et al. 2020; Cervia et al. 2021; Jin et al. 2020; Xiang et al. 2020; Ma et al. 2020; Tang et al. 2021; Zhao et al. 2020; Long et al. 2020; Lynch et al. 2020; Yu et al. 2020). A significant association is seen between these antibodies and prognosis prediction in COVID-19 (Wang et al. 2021). The minimum positive rate of IgM and IgG antibodies reported in different studies was 84.6% and 80.8%, respectively (Lynch et al. 2020); however, the maximum positive rate was 100% for both antibodies (Guo et al. 2020; Lou et al. 2020; Whitman et al. 2020; Cervia et al. 2021; Jin et al. 2020; Xiang et al. 2020; Ma et al. 2020; Tang et al. 2021; Zhao et al. 2020; Long et al. 2020; Lynch et al. 2020; Yu et al. 2020). IgA antibody is less studied than the other two antibodies in COVID-19. In two different studies, the rate of positive IgA antibody in COVID-19 patients was reported to be 98.6% and 99.8% (Ma et al. 2020; Yu et al. 2020). The median seroconversion time for IgM antibody varied from 4 to 18 days in different studies (Guo et al. 2020; Lou et al. 2020; Ma et al. 2020; Tang et al. 2021; Zhao et al. 2020; Long et al. 2020; Lynch et al. 2020; Yu et al. 2020). This range for IgG antibody was 5 to 20 days (Guo et al. 2020; Lou et al. 2020; Ma et al. 2020; Tang et al. 2021; Zhao et al. 2020; Long et al. 2020; Lynch et al. 2020; Yu et al. 2020). The IgA seroconversion time was 4 to 13 days in different studies (Ma et al. 2020 Jul; Yu et al. 2020). The most commonly used methods for antibody measurement in clinical studies were enzyme-linked immunosorbent assay (ELISA), lateral flow immunoassay (LFIA), chemiluminescent microparticle immunoassay (CMIA), and chemiluminescence immunoassay (CLIA) (Guo et al. 2020; Lou et al. 2020; Whitman et al. 2020; Cervia et al. 2021; Jin et al. 2020; Xiang et al. 2020; Ma et al. 2020; Tang et al. 2021; Zhao et al. 2020; Long et al. 2020; Lynch et al. 2020; Yu et al. 2020). Furthermore, many studies have shown a positive correlation between SARS-CoV-2-specific antibody levels and disease outcome in COVID-19 patients (Cervia et al. 2021; Ma et al. 2020; Tang et al. 2021; Lynch et al. 2020; Yu et al. 2020; Lin et al. 2020; Wang et al. 2020; Casadevall et al. 2020).

## Conclusion

In general, it can be concluded that several immune disorders are involved in both COVID-19 and SLE diseases, which in some cases are common to both. These disorders affect almost all parts of the immune system, including the cellular and innate immune systems. Despite numerous studies in this regard, it seems that there are still many unanswered questions about the role of immunity and its disruption in the pathogenesis of both diseases, which necessitates the pursuit of further studies.

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## Declarations

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