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Autoimmunity and autoinflammation in COVID-19: molecular mechanisms and therapeutic strategies

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SUMMARY Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 200 million people worldwide. The mechanisms of immune dysregulation in resulting coronavirus disease 2019 (COVID-19) have not yet been fully elucidated. There is growing evidence to suggest a connection between SARS-CoV-2 infection and the development of autoinflammatory and autoimmune responses. This article will investigate how immune dysregulation in COVID-19 contributes to autoinflammation and autoimmune disease, and discuss the therapeutic implications. Emerging research indicates that the viral infection provokes hyperinflammation by shifting innate and adaptive immune responses towards a proinflammatory state, while suppressing immune regulation. Immune dysregulation and molecular mimicry by SARS-CoV-2 have the potential to break down immunological tolerance, stimulate cross-reactive immune responses, and induce lasting autoimmune disease. Promising immunomodulatory therapies against COVID-19 include treatment with type I and III interferons, antibodies against the virus or inflammatory immune pathways, corticosteroids, cell therapies, immune checkpoint inhibitors, and superantigen therapy. Contextualized by the current research, this article will also address the emerging cases of vaccine-induced immune thrombotic thrombocytopenia (VITT): a rare autoimmune disease elicited by certain SARS-CoV-2 adenoviral vector vaccines. This review exposes the necessity for longitudinal studies investigating the prevalence and persistence of autoinflammatory damage and autoimmune disease following SARS-CoV-2 infection.

INTRODUCTION

There have been over 200 million confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). Approximately 20% of infected individuals develop severe manifestations of coronavirus disease 2019 (COVID-19) (2), characterized by pneumonia, hyperinflammation, coagulopathy, and/or organ damage (2-6). Of note, severe COVID-19 can progress to several life-threatening inflammatory conditions: acute respiratory distress syndrome (ARDS) (5), cytokine storm syndrome (CSS) (3,6), and/or multisystem inflammatory syndrome (MIS-A/C) (18). Six months after symptom onset, a significant portion of recovered individuals continue to experience long-term health consequences in pulmonary and extrapulmonary organ systems (7,8). This chronic illness ("long COVID") has been hypothesized to arise from immunopathological changes in COVID-19 (8).

Immune dysregulation in COVID-19 is evidenced by the induction of a hyperinflammatory state during infection, consisting of elevated levels of proinflammatory cytokines (2,9,10); upregulation of inflammatory cell-mediated responses (2,10); and breakdown of immunological tolerance (2,11,12). This deterioration of self-tolerance by the immune system is a defining feature of autoinflammatory and autoimmune disease (13), and predictably both have been documented during and after SARS-CoV-2 infection.

Autoinflammatory disease is distinguished by transient pathological responses of the *innate* immune system, contrasting with the often-permanent autoimmune disease induced by an autoreactive *adaptive* immune system (14). Non-specific innate responses are largely mediated by inflammatory cytokines, and involve the complement system, monocytes, and granulocytes. In contrast, adaptive responses are antigen-specific and involve cell-mediated

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responses by lymphocytes (2). Dendritic cells (15) and natural killer (NK) cells (16) notably contribute to both innate and adaptive responses. Recent studies are documenting the detrimental effects of SARS-CoV-2 on both the innate and adaptive arms of the immune system, contributing to autoinflammatory and autoimmune disease (2,9,10).

Autoinflammatory consequences during SARS-CoV-2 infection include encephalopathy (2,11,17); (cardio)myopathy (2,11); vasculitis (2,11); coagulopathy (2,11,21); and systemic illnesses such as ARDS (5), CSS (3,6), and MIS-A/C (18) (see Fig. 1A). Alarmingly, there are emerging reports of viral-induced autoimmune disease following SARS-CoV-2 clearance, such as systemic lupus erythematosus, type I diabetes (19), and antiphospholipid syndrome (2,19,21) (Fig. 1B).

Cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have been documented following administration of the SARS-CoV-2 adenoviral vector vaccines AZD1222 (AstraZeneca), COVISHIELD (Serum Institute of India), and Ad26.COV2.S (Janssen). The incidence of VITT is 1 in 100,000 (AstraZeneca/Serum Institute of India) to 1 in 500,000 (Janssen) doses (23), with an estimated 40% mortality rate (24). A tentative mechanism for the disorder has been described: all VITT patients tested positive for anti-platelet factor 4 (PF4) autoantibodies (24). Why certain SARS-CoV-2 adenoviral vector vaccines lead to the development of anti-PF4 antibodies in VITT remains unknown.

The complex dynamics involving immune dysregulation by SARS-CoV-2 are not yet well-understood. Given that pathogenic autoimmune and autoinflammatory responses underlie many of the severe events that occur during and after SARS-CoV-2 infection (Fig. 1), there is growing interest in the use of immunomodulatory drugs against COVID-19.

PROPOSED RESEARCH QUESTIONS

While the autoinflammatory and autoimmune manifestations observed in COVID-19 are well-documented (Fig. 1), the underlying mechanisms of immune dysregulation have not been fully elucidated. This article will investigate how immune dysregulation in COVID-19 contributes to autoinflammatory and autoimmune disease, during and after viral infection. In dissecting the immunopathology of COVID-19, this review aims to find therapeutic strategies that limit the long-term damaging effects of autoimmunity and autoinflammation induced by this viral infection. Given the research described here, this article will also address the emerging cases of VITT following administration of certain SARS-CoV-2 vaccines.

PROPOSED PROJECT NARRATIVE

How does immune dysregulation contribute to autoinflammation in COVID-19? Given the autoinflammatory manifestations in severe COVID-19 (Fig. 1A), it is imperative to understand the immune dysregulation underlying these effects - mechanisms which have yet to be fully elucidated. Immune profiling of moderate to severe COVID-19 patients shows decreased B, $CD4^+$/$CD8^+$ T, and NK cells (i.e. lymphopenia). This suppression of adaptive immune responses is contrasted by elevated monocytes, neutrophils, and eosinophils of the innate immune system (2,10). Transcriptional and serum profiling of COVID-19 patients consistently shows elevated levels of inflammatory cytokines and chemokines associated with the innate immune system (Table 1), juxtaposed with dampened antiviral type I and III interferon (IFN) production (25). The elevated cytokine profile in severe COVID-19 bears similarity to CSS in SARS-CoV-1 and MERS (26). These data demonstrate that COVID-19 is characterized by a shift away from targeted adaptive immunity and interferon responses, towards inflammatory and non-specific innate immunity.

Dampening of adaptive responses by SARS-CoV-2 inhibits the potent antiviral response of lymphocytes, promoting the autoinflammatory effects of the virus. In addition to the depletion of B, $CD4^+$/$CD8^+$ T, and NK cells (2,10), COVID-19 is characterized by decreased T helper memory cells, inhibiting secondary responses to future viral infection (2). Several cytokines that are elevated in COVID-19 have been implicated in suppression of NK and T regulatory (T_{reg}) cells (Table 1). Additionally, autopsy findings in COVID-19 patients uncovered destruction of secondary lymphoid tissues, with spleen and lymph node atrophy. Among CSS-associated diseases, this is a feature unique to COVID-19 (26).

Despite the reduction in overall lymphocyte counts, COVID-19 patients experience hyperactivation of remaining cytotoxic and helper T cells. This is evidenced by the increased expression of $CD4^+$/$CD8^+$ T cell activation markers (HLA-DR (26), CD38 or CD44 (2)), as well as increased cytotoxic perforin and granulysin in $CD8^+$ T cells (26). Among the cytotoxic $CD8^+$ fraction of T cells, there is an increased proportion of $PD1^+Tim3^+$ cells and elevated NKG2A expression, indicating T cell exhaustion (2). Further, this rampant hyperactivation of cytotoxic and helper T cells is left unchecked, due to the inhibition of regulatory T cells. COVID-19 patients exhibit decreased levels of $CD28^+$ cytotoxic suppressor and T_{reg} cells, impairing the suppression of hyperactivated and autoreactive T cells, with the potential to induce autoinflammation and autoimmune disease (2).

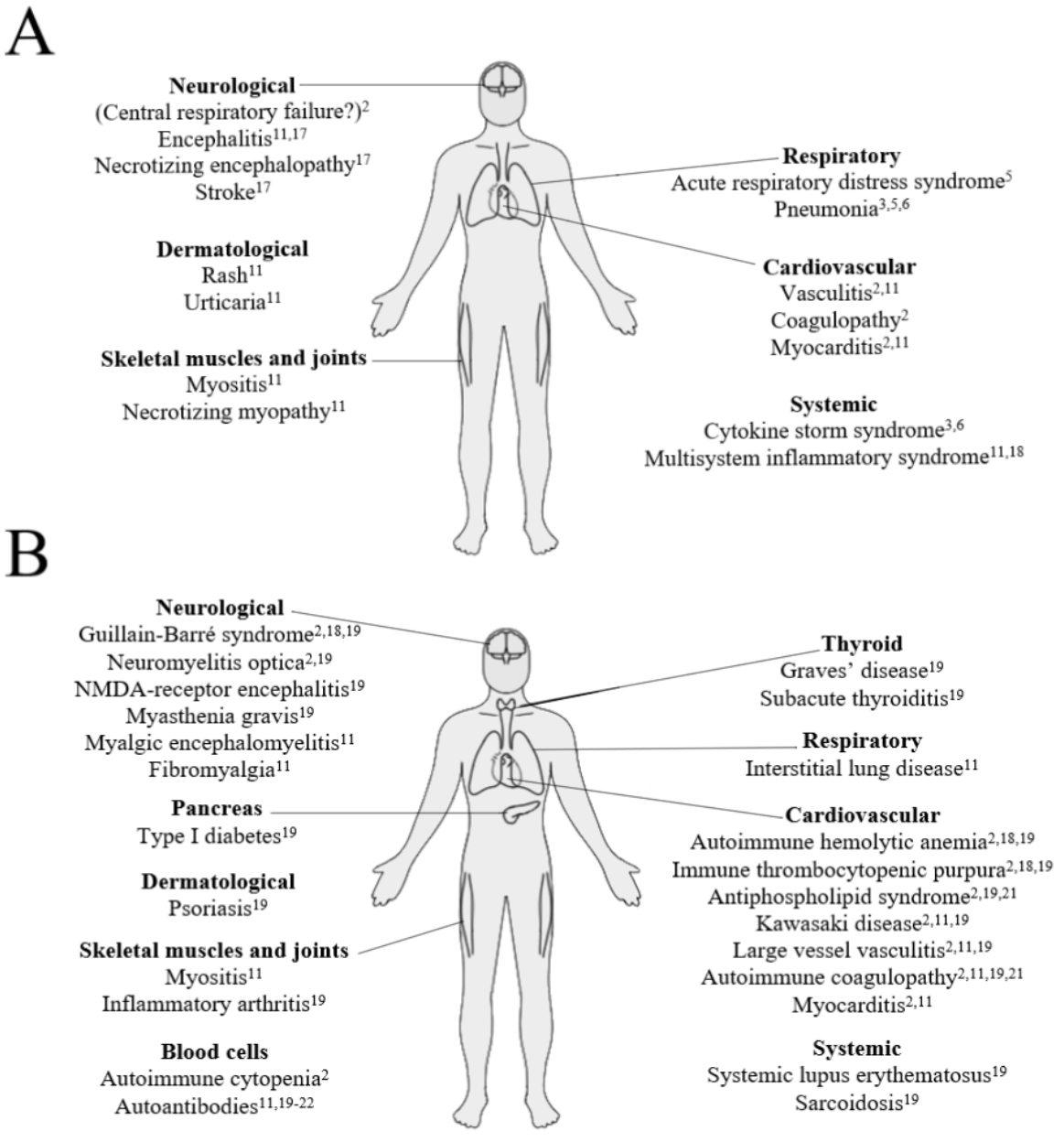

FIG. 1 Autoinflammatory (A) and autoimmune (B) conditions documented during and after SARS-CoV-2 infection.

Despite decreased $CD4^+$ helper T cell counts in COVID-19, the proportions of proinflammatory T helper 1 (T_h1) and T helper 17 (T_h17) cells are elevated. Both T_h1 and T_h17 responses are implicated in the production of certain proinflammatory cytokines observed in severe COVID-19 and CSS (2,10,11,26) (Table 1). This phenotype of elevated

T_h1/T_h17 responses, hyperactivation of $CD8^+$ T cells, and decreased regulatory T cells has been described in the development of multiple autoinflammatory and autoimmune diseases (2,11).

The elevation of IL-1β and IL-18 in COVID-19 (Table 1) points to an additional mechanism of hyperinflammation: inflammasome activation. Assembly of inflammasomes—multiprotein complexes of the innate immune system—activates inflammatory cytokines IL-1β and IL-18, while inducing pyroptosis of the cell. SARS-CoV-2 infection has been documented to activate the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome in peripheral blood mononuclear cells (PBMCs) and tissues of infected patients, positively correlating with the severity of COVID-19 (27). In essence, inflammasome activation contributes to the hyperinflammatory state in COVID-19.

TABLE 1 Elevated cytokines and chemokines identified in COVID-19 patients.

Proinflammatory responses				**Immunosuppressive responses**	
Immune recruitment	**Innate immune system**	**Adaptive immune system**			
Inflammatory chemokines	**Inflammatory cytokines**	**T_h1 responses**	**T_h17 responses**	**NK cell inhibition**	**T_{reg} cell inhibition**
CCL2[2,9,10]	IL-1β[2,9,10]	IL-1β[2,9,10]	IL-1β[2,9,10]	NKG2A[2]	IL-1β[2,9,10]
CCL3[2,9]	IL-6[2,9,10]	IL-2[2,9]	IL-6[2,9,10]		IL-6[2,9,10]
CCL4[4]	IL-8[2]	IL-7[2,9]	IL-7[2,9]		
CCL5[2,10]	IFNα[2,10]	IL-12[9,10]	IL-8[2]		
CCL7[2]	IFNγ[2,9]	IL-18[10]	IL-17[9,10]		
CXCL2[2]	TNF-α[2,9]	IL-33[10]	IL-21[10]		
CXCL8[2]	G-CSF[2,9]	IFNγ[2,9,10]	IL-22[10]		
CXCL9[2]	M-CSF[9]	TNF-α[2,9,10]	IL-33[10]		
CXCL10[2,9,10]	GM-CSF[2,9]	GM-CSF[2,9]	TNF-α[2,9]		
			G-CSF[2,9]		
			GM-CSF[2,9]		

Abbreviations

CCL	CC-chemokine ligand
CXCL	CXC-chemokine ligand
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IFN	Interferon
IL	Interleukin
MIP	Macrophage inflammatory protein
NKG2A	Natural killer group 2 member A
TNF	Tumour necrosis factor

Current studies are identifying a growing collection of autoantibodies in COVID-19 patients, implicated in autoimmune diseases that have been documented following infection (Table 2) (11,19-22). Certain autoantibodies occur with alarming frequency in severe COVID-19. Anti-phospholipid antibodies were found in 52% of hospitalized COVID-19 patients - diagnostic of the life-threatening thrombophilia, antiphospholipid syndrome (21).

Franke *et al.* found that all study patients with neurological manifestations of COVID-19 possessed autoantibodies against neural or endothelial tissues (22). While there is abundant evidence for autoimmune antibody responses, autoreactive T cells induced by SARS-CoV-2 have yet to be identified.

TABLE 2 Autoantibodies and associated autoimmune diseases documented in COVID-19 patients.

Autoantibodies	Associated autoimmune diseases in COVID-19 patients
Anti-annexin V IgM/IgG[19,22]	Autoimmune coagulopathy (hypo-/hypercoagulation)[19,21]
Anti-cardiolipin[19,21,22]	Autoimmune cytopenia[19,21]
Anti-CCP[19]	Autoimmune neurological disease[19,22]
Anti-GD1b[19]	Autoimmune thyroid disease[19]
Anti-heparin/PF4 complex[19]	Autoimmune vasculitis[11,19]
Anti-interferon (type I)[20]	Dampened interferon responses[20]
Anti-MDA5[19]	Dermatomyositis[19]
Anti-myelin[22]	Inflammatory arthritis[19]
Anti-NMDAR IgG[22]	Psoriasis[19]
Anti-nuclear antigen (ANA)[19]	Sarcoidosis[19]
Anti-phosphatidylserine IgM/IgG[19,21]	Systemic lupus erythematosus[19]
Anti-prothrombin IgM[19,21]	Type I diabetes[19]
Anti-RBC[19]	
Anti-Yo[22]	
Anti-β2 glycoprotein 1 (aβ2GP1)[19,21,22]	
Lupus anticoagulant[19]	
pANCA and cANCA[19]	

Abbreviations

(p/c)ANCA	(Perinuclear/cytoplasmic) anti-neutrophil cytoplasmic antibodies
CCP	Cyclic citrullinated peptide
GD1b	Ganglioside GD1b
Ig(A/D/E/G/M)	Immunoglobulin
MDA5	Melanoma differentiation-associated protein 5
PF4	Platelet factor 4
RBC	Red blood cell

Lastly, the SARS-CoV-2 spike (S) glycoprotein bears a striking similarity to known superantigens. Superantigens potently activate $CD4^+/CD8^+$ T cells by binding to T cell receptors (TCRs) in an antigen-independent manner. This ability to broadly and non-specifically activate T cells leads to the excessive release of proinflammatory cytokines, resulting in a cytokine storm (CSS, MIS-A/C, or toxic shock syndrome). A unique $P_{681}RRA_{684}$ insertion in SARS-CoV-2—just prior to the furin cleavage site—is not found in other SARS β-coronaviruses. This insertion has created a motif of ~20 amino acids with strong sequence and structural similarity to the superantigen staphylococcal enterotoxin B (SEB). Effectively, the S glycoprotein may induce a cytokine storm via superantigen T cell activation in COVID-19 (28).

In conclusion, dysregulation of the immune system by SARS-CoV-2 induces autoinflammation during infection, with the potential to cause lasting inflammatory damage, autoimmune disease, and death. The virus shifts innate and adaptive immune responses towards a proinflammatory state while simultaneously suppressing immune regulation, consequently provoking an autoinflammatory response.

How does immune dysregulation contribute to the development of autoimmune disease in COVID-19? Given that immune dysregulation by SARS-CoV-2 induces autoinflammation, it is also pertinent to investigate the development of autoimmune disease following infection. SARS-CoV-2 has been proposed to cause autoimmunity via four main mechanisms: 1) molecular mimicry, 2) bystander activation with epitope spreading, 3) breakdown of self-tolerance, and 4) inflammasome activation.

Molecular mimicry occurs when viral antigens share similarity to self-antigens, provoking a cross-reactive adaptive immune response against host tissues (11,29). Studies have identified numerous SARS-CoV-2 penta-/hexapeptides (epitopes) with identical matches to human proteins. These peptides could be displayed on MHC I and II complexes during viral infection, subsequently inducing cross-reactive autoimmune responses. Antibodies against the SARS-CoV-2 S glycoprotein have strong immune cross-reactions (≥33% binding efficiency relative to S glycoprotein) with the human proteins transglutaminase (tTG) 2, tTG3, extractable and anti-nuclear antigen (ENA/ANA), myelin basic protein (MBP), mitochondria, α-myosin, thyroid peroxidase (TPO), collagen, claudin 5, claudin 6, and S100β. With antibodies against SARS-CoV-2 nucleoprotein, comparable cross-reactions (≥33% binding efficiency relative to nucleoprotein) occur with tTG6, α-myosin, ENA/ANA, mitochondria, and TPO (30). Additionally, computational analysis identified viral peptides that potentially cross-react with pulmonary surfactant (and related) proteins to induce autoimmune lung damage. Other SARS-CoV-2 peptides bear similarity to the pre-Bötzinger complex (brainstem respiratory pacemaker) - this cross-reaction is hypothesized to account for the central respiratory depression observed in ARDS (2).

Bystander activation is the antigen-independent activation of the adaptive immune system via cytokines, leading to the diversification of epitope specificity (epitope spreading) (2,11). Gregorova *et al.* identified a patient with bystander activation of T cells specific against SARS-CoV-2 during recurrent microbial infections (31). This indicates that T cells specific against the virus are capable of activation in the absence of viral antigens, simply by the elevated presence of inflammatory cytokines. Of note, inflammatory cytokines are elevated in COVID-19 (2,9,10), and the elevated cytokine IL-2 has been shown to mediate bystander activation (2). This antigen-independent activation of T cells could result in the cloning of other T cell epitopes, with the eventual diversification of their specificity to include host tissues. In essence, the inflammatory cytokine profile of COVID-19 creates the ideal environment for bystander activation and epitope spreading.

As discussed earlier in this article, breakdown of self-tolerance can occur by the depletion of $CD28^+$ cytotoxic suppressor and T_{reg} cells in COVID-19, permitting autoimmune T and B cell responses to persist unchecked (2). This manifests as autoantibodies (11,19-22), hyperactivated T cells (2,26), and potentially autoreactive T cells in COVID-19.

Activation of the NLRP3 inflammasome by SARS-CoV-2 (27) provokes an inflammatory cascade and activates naïve T cells. Notably, excessive activation of NLRP3 has been implicated in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Behçet's disease, Sjögren's syndrome, gout, and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (32). Thus, it is reasonable to conclude that inflammasome activation by SARS-CoV-2 could potentially contribute to the development of autoimmunity. In summary, immune responses against SARS-CoV-2 have the potential to cross-react with human tissues, inducing lasting autoimmune disease.

What are the therapeutic implications of autoinflammatory and autoimmune responses in COVID-19? Understanding immune dysregulation in COVID-19 allows us to direct the development of immunomodulatory therapeutics against the disease. Potential therapies include treatment with type I and III IFNs (33), antibodies against the virus (37,40) or

inflammatory immune pathways (33-35,39), corticosteroids (36), cell therapies, immune checkpoint inhibitors (33), and superantigen therapy (28).

As type I and III IFNs are downregulated in COVID-19, treatments with IFN-α, IFN-β, and IFN-λ have entered phase I-IV clinical trials. IFN therapy has the potential to stimulate a potent antiviral response in early infection, but is contraindicated in later severe infection (33).

Immunomodulatory treatments for the management of severe COVID-19 include antibody blockade of cytokine and complement pathways, as well as immunosuppression by corticosteroids. Elevated IL-1β, IL-6, and TNF-α are critical in the development of CSS, and antibody inhibitors against these and other proinflammatory targets (Janus kinase (JAK), GM-CSF, IL-17, IFN-γ, complement C3/C5) have entered phase I-IV clinical trials (33). Given the current clinical data, the National Institutes of Health's (NIH) treatment guidelines recommend the use of a corticosteroid (dexamethasone), IL-6 inhibitor (tocilizumab), and/or JAK-inhibitor (baricitinib) in severe COVID-19 (34). Systematic meta-analyses showed that COVID-19 patient mortality significantly decreases with the use of IL-6 inhibitors (27 trials, pooled odds ratio [OR] 0.86) (35) and JAK-inhibitors (11 studies, pooled relative risk [RR] 0.42) (36). The use of corticosteroids such as dexamethasone is indicated in severe COVID-19 for the treatment of hyperinflammation and ARDS. A meta-analysis of 44 studies found that corticosteroids significantly reduce the risk of COVID-19 mortality (pooled OR 0.72) (37). Corticosteroids, IL-6 inhibitors, and JAK-inhibitors tentatively appear most effective in treating hyperinflammation and CSS, however this may change as new research emerges.

Passive antibody-based immunotherapies have been widely used to treat SARS-CoV-2 infection. Convalescent plasma is commonly used in patient treatment, however a recent meta-analysis found that its use is not associated with significant clinical improvements or a decrease in mortality (38). Intravenous immunoglobulin (IVIG) therapy—consisting of pooled polyclonal IgG antibodies from many donors—has entered phase I-IV clinical trials (33). IVIG therapy dampens hyperactive immune responses while also potentially neutralizing viral particles (39). Monoclonal antibodies against the SARS-CoV-2 S glycoprotein receptor-binding domain (RBD) have been granted Emergency Use Authorization, and significantly reduced viral load in clinical trials (40). Monoclonal antibody therapy appears promising thus far.

Several cell therapies have entered early clinical trials in the treatment of COVID-19: macrophage, dendritic, NK, T, and mesenchymal stem cell therapy (33). Widespread use of cell therapy does not appear feasible at this time: challenges of cellular expansion and transplantation include time, resource, and cost requirements. In addition, there are safety concerns regarding the genomic instability and regenerative capacity of expanded cells (41). Immune checkpoint inhibitors of proteins such as VEGF, CD14, and T cell exhaustion markers (PD1, Tim3, NKG2A) are also under consideration for COVID-19 (33). Given the research described in this article, it should be noted that inhibition of T cell exhaustion markers could *worsen* autoinflammation and autoimmunity in COVID-19, as this may promote the development of hyperactivated and autoreactive T cells (2).

The research in this review suggests additional therapies that could be developed in the treatment of COVID-19. The implication that the S glycoprotein may act as a superantigen indicates the potential benefit of superantigen therapies: treatments against SEB-mediated TSS and inhibition of the S glycoprotein-TCR interaction may reduce hyperinflammation in COVID-19 (28). There are also implications about the potential risks of existing therapies. Patients using drugs that impair B cell function and neutralizing antibody production (e.g. CD20, IL-17A inhibitors) are at increased risk of severe COVID-19 (2).

Studies have identified numerous SARS-CoV-2 epitopes with matches to human proteins, suggesting that autoimmune cross-reactions can occur via molecular mimicry (2). Given this information, it would be reasonable to hypothesize that the S glycoprotein conformation in certain vaccines may induce anti-PF4 autoantibodies (i.e. VITT). Notably, SARS-CoV-2 has been implicated in the production of anti-PF4/heparin autoantibodies, as well as the development of thrombosis and autoimmune thrombocytopenia (19). Despite this, a recent study (preprint) has countered S glycoprotein molecular mimicry as a potential cause of VITT: antibodies against the viral protein do not cross-react with PF4 (42). Reports have alternatively speculated that free DNA and RNA in these vaccines could be responsible for

the generation of anti-PF4 autoantibodies (24). In conclusion, the component of certain SARS-CoV-2 vaccines that results in the development of VITT remains an important question for future investigation.

CONCLUSIONS

As the mechanisms of immune dysregulation in COVID-19 emerge, additional questions arise. Which host factors influence susceptibility to severe immunopathology in COVID-19? Immune factors such as HLA polymorphisms have been implicated in the severity and susceptibility to SARS-CoV-2 infection (43). Additionally, are certain variants of SARS-CoV-2 associated with more severe immunopathology? This would require further research into how specific viral factors contribute to the immune dysregulation observed in COVID-19.

This article exposes the necessity for longitudinal studies investigating the prevalence and persistence of autoinflammatory and autoimmune manifestations of COVID-19. However, it may be challenging to conclusively prove viral-induced autoimmune disease. Proposed strategies include: 1) cross-referencing severity of infection with incidence of autoimmune disease; 2) comparing the incidence of autoimmune disease in vaccinated versus unvaccinated individuals; and 3) testing patients with autoimmune disease for T cells and antibodies that cross-react between SARS-CoV-2 and self-antigens (e.g. myelin).

Given that the elevation of certain proinflammatory cytokines and chemokines is associated with severe COVID-19, there is potential to use these molecules as prognostic markers. Recent studies suggest using IL-6, IL-10, and TNF-α levels as the primary predictors of disease severity and death (44,45). With further research, these markers could be routinely employed in hospital testing.

Immunodeficient or immunocompromised individuals are vulnerable to severe COVID-19, and this is generally accounted for in immunization plans. Based on the research described in this article, there is a need to prioritize additional populations for vaccination. Such populations include individuals taking B-cell inhibitors (2) and individuals with pre-existing lymphopenia (46), as severe COVID-19 is characterized by (T/B/NK cell) lymphopenia. Additionally, 10.2% of critically ill COVID-19 patients possess pre-existing autoantibodies against type I IFNs, and thus individuals with this immune vulnerability should also be prioritized for vaccination (20).

In conclusion, immune dysregulation in COVID-19 is responsible for many of the autoinflammatory and autoimmune manifestations observed during and after infection. The viral infection shifts immune responses towards a proinflammatory state while suppressing immune regulation, provoking a hyperinflammatory state. Immune dysregulation and molecular mimicry by SARS-CoV-2 has the potential to break down immunological tolerance and induce lasting autoimmune disease in some individuals. Fortunately, emerging immunomodulatory drugs and vaccination show promise in the treatment and prevention of COVID-19. It is crucial for virologists to collaborate closely with immunologists and rheumatologists on future COVID-19 research: the pathology of COVID-19 is intricately linked to immune dysregulation.

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REFERENCES

1. **World Health Organization**. 2021 Aug 10. Weekly epidemiological update on COVID-19. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
2. **Rodríguez Y, Novelli L, Rojas M, De Santis M, Acosta-Ampudia Y, Monsalve DM, Ramírez-Santana C, Costanzo A, Ridgway WM, Ansari AA, Gershwin ME, Selmi C, Anaya J.** 2020. Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. *J Autoimmun* **114:**102506.

3. **Gustine JN, Jones D.** 2021. Immunopathology of Hyperinflammation in COVID-19. *Am J Pathol* **191:**4-17.
4. **Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP.** 2020. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* **20:**363-374.
5. **Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y.** 2020. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* **180:**934-943.
6. **Elezkurtaj S, Greuel S, Ihlow J, Michaelis EG, Bischoff P, Kunze CA, Sinn BV, Gerhold M, Hauptmann K, Ingold-Heppner B, Miller F, Herbst H, Corman VM, Martin H, Radbruch H, Heppner FL, Horst D.** 2021. Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci Rep* **11:**4263.
7. **Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, Cao B.** 2021. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* **397:**220-232.
8. **Al-Aly Z, Xie Y, Bowe B.** 2021. High-dimensional characterization of post-acute sequalae of COVID-19 [published online ahead of print, 22 Apr 2021]. *Nature* **594**(7862):259-264.
9. **Costela-Ruiz V, Illescas-Montes R, Puerta-Puerta J, Ruiz C, Melguizo-Rodríguez L.** 2020. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev* **54:**62-75.
10. **Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, Ellingson MK, Mao T, Oh JE, Israelow B, Takahashi T, Tokuyama M, Lu P, Venkataraman A, Park A, Mohanty S, Wang H, Wyllie AL, Vogels CBF, Earnest R, Lapidus S, Ott IM, Moore AJ, Muenker MC, Fournier JB, Campbell M, Odio CD, Casanovas-Massana A, Obaid A, Lu-Culligan A, Nelson A, Brito A, Nunez A, Martin A, Watkins A, Geng B, Kalinich C, Harden C, Todeasa C, Jensen C, Kim D, McDonald D, Shepard D, Courchaine E, White EB, Song E, Silva E, Kudo E, DeIuliis G, Rahming H, Park H, Matos I, Nouws J, Valdez J, Fauver J, Lim J, Rose K, Anastasio K, Brower K, Glick L, Sharma L, Sewanan L, Knaggs L, Minasyan M, Batsu M, Petrone M, Kuang M, Nakahata M, Campbell M, Linehan M, Askenase MH, Simonov M, Smolgovsky M, Sonnert N, Naushad N, Vijayakumar P, Martinello R, Datta R, Handoko R, Bermejo S, Prophet S, Bickerton S, Velazquez S, Alpert T, Rice T, Khoury-Hanold W, Peng X, Yang Y, Cao Y, Strong Y, Herbst R, Shaw AC, Medzhitov R, Schulz WL, Grubaugh ND, Dela Cruz C, Farhadian S, Ko AI, Omer SB, Iwasaki A, Yale IT.** 2020. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* **584:**463-469.
11. **Talotta R, Robertson E.** 2020. Autoimmunity as the comet tail of COVID-19 pandemic. *World J Clin Cases* **8**(17):3621-3644.
12. **Gregorova M, Morse D, Brignoli T, Steventon J, Hamilton F, Albur M, Arnold D, Thomas M, Halliday A, Baum H, Rice C, Avison MB, Davidson AD, Santopaolo M, Oliver E, Goenka A, Finn A, Wooldridge L, Amulic B, Boyton RJ, Altmann DM, Butler DK, McMurray C, Stockton J, Nicholls S, Cooper C, Loman N, Cox MJ, Rivino L, Massey RC.** Post-acute COVID-19 associated with evidence of bystander T-cell activation and a recurring antibiotic-resistant bacterial pneumonia. *Elife* **9:**e63430.
13. **Sinha AA, Lopez MT, McDevitt HO.** 1990. Autoimmune diseases: the failure of self tolerance. *Science* **248**(4961):1380-1388.
14. **Doria A, Zen M, Bettio S, Gatto M, Bassi N, Nalotto L, Ghirardello A, Iaccarino L, Punzi L.** 2012. Autoinflammation and autoimmunity: Bridging the divide. *Autoimmun Rev: Autoinflammatory Days* **12:**22-30.
15. **Steinman RM.** 2006. Linking innate to adaptive immunity through dendritic cells. *Novartis Found Symp* **279:**101-219.
16. **Moretta A, Marcenaro E, Parolini S, Ferlazzo G, Moretta L.** 2008. NK cells at the interface between innate and adaptive immunity. *Cell Death Differ* **15**(2):226-233.
17. **Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T.** 2020. Neurological associations of COVID-19. *Lancet Neurol* **19:**767-783.
18. **Galeotti C, Bayry J.** 2020. Autoimmune and inflammatory diseases following COVID-19. *Nat Rev Rheumatol* **16**(8):413-414.
19. **Halpert G, Shoenfeld Y**. 2020. SARS-CoV-2, the autoimmune virus. *Autoimmun Rev* **19**(12):102695.
20. **Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Béziat V, Manry J, Shaw E, Haljasmägi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Le Pen J, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, Abers MS, Aiuti A, Casari G, Lampasona V, Piemonti L, Ciceri F, Bilguvar K, Lifton RP, Vasse M, Smadja DM, Migaud M, Hadjadj J, Terrier B, Duffy D, Quintana-Murci L, van de Beek D, Roussel L, Vinh DC, Tangye SG, Haerynck F, Dalmau D, Martinez-Picado J, Brodin P, Nussenzweig MC, Boisson-Dupuis S, Rodríguez-Gallego C, Vogt G, Mogensen TH, Oler AJ, Gu J, Burbelo PD, Cohen JI, Biondi A, Bettini LR, D'Angio M, Bonfanti P,**

Rossignol P, Mayaux J, Rieux-Laucat F, Husebye ES, Fusco F, Ursini MV, Imberti L, Sottini A, Paghera S, Quiros-Roldan E, Rossi C, Castagnoli R, Montagna D, Licari A, Marseglia GL, Duval X, Ghosn J, HGID Lab, NIAID-USUHS Immune Response to COVID Group, COVID Clinicians, COVID-STORM Clinicians, Imagine COVID Group, French COVID Cohort Study Group, Milieu Intérieur Consortium, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, Tsang JS, Goldbach-Mansky R, Kisand K, Lionakis MS, Puel A, Zhang SY, Holland SM, Gorochov G, Jouanguy E, Rice CM, Cobat A, Notarangelo LD, Abel L, Su HC, Casanova JL. 2020. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **370:**eabd4585.

21. **Zuo Y, Estes SK, Ali RA, Gandhi AA, Yalavarthi S, Shi H, Sule G, Gockman K, Madison JA, Zuo M, Yadav V, Wang J, Woodard W, Lezak SP, Lugogo NL, Smith SA, Morrissey JH, Kanthi Y, Knight JS.** 2020. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. *Sci Transl Med* **12**(570):eabd3876.
22. **Franke C, Ferse C, Kreye J, Reincke SM, Sanchez-Sendin E, Rocco A, Steinbrenner M, Angermair S, Treskatsch S, Zickler D, Eckardt KU, Dersch R, Hosp J, Audebert HJ, Endres M, Ploner JC, Prüß H.** 2021. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain Behav Immun* **93**:415-419.
23. **Pai M, Chan B, Stall NM, Grill A, Ivers N, Maltsev A, Miller KJ, Odutayo A, Razak F, Schull M, Schwartz B, Sholzberg M, Steiner R, Wilson S, Neil U, Juni P, Morris AM.** 2021. Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination. *Science Briefs of the Ontario COVID-19 Science Advisory Table* **2**:17.
24. **Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S.** 2021. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med* **384**(22):2092-2101.
25. **Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT.** 2020. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell* **181**(5):1036-1045.
26. **Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S.** 2020. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clin Immunol* **214:**108393.
27. **Rodrigues TS, de Sá KSG, Ishimoto AY, Becerra A, Oliveira S, Almeida L, Gonçalves AV, Perucello DB, Andrade WA, Castro R, Veras FP, Toller-Kawahisa JE, Nascimento DC, de Lima MHF, Silva CMS, Caetite DB, Martins RB, Castro IA, Pontelli MC, de Barros FC, do Amaral NB, Giannini MC, Bonjorno LP, Lopes MIF, Santana RC, Vilar FC, Auxiliadora-Martins M, Luppino-Assad R, de Almeida SCL, de Oliveira FR, Batah SS, Siyuan L, Benatti MN, Cunha TM, Alves-Filho JC, Cunha FQ, Cunha LD, Frantz FG, Kohlsdorf T, Fabro AT, Arruda E, de Oliveira RDR, Louzada-Junior P, Zamboni DS.** 2021. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. *J Exp Med* **218**(3):e20201707.
28. **Cheng MH, Zhang S, Porritt RA, Noval Rivas M, Paschold L, Willscher E, Binder M, Arditi M, Bahar I.** 2020. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. *Proc Natl Acad Sci USA* **117:**25254.
29. **Cusick MF, Libbey JE, Fujinami RS.** Molecular mimicry as a mechanism of autoimmune disease. *Clin Rev Allergy Immunol* **42**(1):102-111.
30. **Vojdani A, Kharrazian D.** 2020. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin Immunol* **217:**108480.
31. **Gregorova M, Morse D, Brignoli T, Steventon J, Hamilton F, Albur M, Arnold D, Thomas M, Halliday A, Baum H, Rice C, Avison MB, Davidson AD, Santopaolo M, Oliver E, Goenka A, Finn A, Wooldridge L, Amulic B, Boyton RJ, Altmann DM, Butler DK, McMurray C, Stockton J, Nicholls S, Cooper C, Loman N, Cox MJ, Rivino L, Massey RC.** 2020. Post-acute COVID-19 associated with evidence of bystander T-cell activation and a recurring antibiotic-resistant bacterial pneumonia. *Elife* **9:**e63430.
32. **Shin JI, Lee KH, Joo YH, Lee JM, Jeon J, Jung HJ, Shin M, Cho S, Kim TH, Park S, Jeon BY, Jeong H, Lee K, Kang K, Oh M, Lee H, Lee S, Kwon Y, Oh GH, Kronbichler A.** 2019. Inflammasomes and autoimmune and rheumatic diseases: A comprehensive review. *J Autoimmun* **103:**102299.
33. **Esmaeilzadeh A, Elahi R.** 2021. Immunobiology and immunotherapy of COVID-19: A clinically updated overview. *J Cell Physiol* **236**(4):2519-2543.
34. **National Institutes of Health: COVID-19 Treatment Guidelines Panel.** 2021 Aug 4. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: Immunomodulators Under Evaluation for the Treatment of COVID-19. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/summary-recommendations/.
35. **The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group.** 2021. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA* **326**:499–518.
36. **Chen CX, Wang JJ, Li H, Yuan LT, Gale RP, Liang Y.** 2021. JAK-inhibitors for coronavirus disease-2019 (COVID-19): a meta-analysis [published online ahead of print, 14 May 2021]. *Leukemia* 1–5.

37. **van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM.** 2020. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care* **24:**696.
38. **Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, Smith ER, Haber NA, Khanna N, Moher D, Goodman SN, Ioannidis JPA, Hemkens LG.** 2021. Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. *JAMA* **325:**1185-1195.
39. **Tzilas V, Manali E, Papiris S, Bouros D.** 2020. Intravenous Immunoglobulin for the Treatment of COVID-19: A Promising Tool. *Respiration* **99**(12):1087-1089.
40. **Cohen, MS.** 2021. Monoclonal Antibodies to Disrupt Progression of Early Covid-19 Infection. *N Engl J Med* **384:**289-291.
41. **Choudhery MS, Harris DT.** 2020. Stem cell therapy for COVID-19: Possibilities and challenges. *Cell Biol Int* **44**(11):2182-2191.
42. **Greinacher A, Selleng K, Mayerle J, Palankar R, Wesche J, Reiche S, Aebischer A, Warkentin TE, Muenchhoff M, Hellmuth JC, Keppler OT, Duerschmied D, Lother A, Rieg S, Meinrad PG, Karin Anne LM, Scheer CS, Napp M, Hahnenkamp K, Lucchese G, Vogelgesang A, Flöel A, Lovreglio P, Stufano A, Marschalek R, Thiele T.** 2021. Anti-SARS-CoV-2 Spike Protein and Anti-Platelet Factor 4 Antibody Responses Induced by COVID-19 Disease and ChAdOx1 nCov-19 vaccination [Preprint]. *Research Square*. doi: 10.21203/rs.3.rs-404769/v1.
43. **Tavasolian F, Rashidi M, Hatam GR, Jeddi M, Hosseini AZ, Mosawi SH, Abdollahi E, Inman RD.** 2021. HLA, Immune Response, and Susceptibility to COVID-19. *Front Immunol* **11:**601886.
44. **Del Valle DM, Kim-Schulze S, Huang H, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, Marron TU, Xie H, Patel M, Tuballes K, Van Oekelen O, Rahman A, Kovatch P, Aberg JA, Schadt E, Jagannath S, Mazumdar M, Charney AW, Firpo-Betancourt A, Mendu DR, Jhang J, Reich D, Sigel K, Cordon-Cardo C, Feldmann M, Parekh S, Merad M, Gnjatic S.** 2020. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* **26:**1636-1643.
45. **Dhar SK, K V, Damodar S, Gujar S, Das M.** 2021. IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression. *Heliyon* **7:**e06155.
46. **Burack WR, Rock P, Burton D, Cai X.** 2020. Association of pre-COVID-19 lymphocytopenia with fatality [Preprint]. *medRxiv*. doi: 10.1101/2020.10.02.20200931