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Mini review

Is COVID 19, a beginning of new entity called chronic viral systemic inflammatory syndrome?

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Abstract: Since the emergence of SARS-COV-2, many updates and assumptions are being discussed based on the emerging understanding of the pathophysiology and outcomes of the infection. The host immune response is the critical factor in disease severity and the unique immune response of each individual has resulted in a broad spectrum of disease severity and clinical presentations. In this article, combining the emerging knowledge on the immunopathogenesis of COVID-19 infection with insights into the underlying mechanisms of certain autoimmune and chronic Immune-mediated inflammatory diseases we propound our hypothesis that SARS-CoV-2 infection produces chronic viral inflammatory syndrome.

Keywords: COVID-19; chronic viral inflammatory syndrome; cytokines; immune-mediated inflammatory disease; NLRP3 activation; senescent activated secretory phenotype

Abbreviations: DAB1: disabled homolog 1; SURF1: surfeit locus protein 1; AIFM: apoptosis-inducing factor mitochondrial; TIM-3: T cell immunoglobulin and mucin domain 3; CTLA4: cytotoxic T lymphocyte associated protein 4; PD1: programmed cell death protein 1; TIGIT: T cell immunoglobulin and ITIM domain receptor; MAVS: mitochondrial antiviral signaling proteins; VDAC: voltage dependent anion channel; ACE II: angiotensin converting enzyme II; AT1R: angiotensin I receptor; NLRP3: nuclear NOD, LRR, pyrin domain containing protein 3; IL: interleukin; GMCSF: granulocyte monocyte colony stimulating factor; TNF: tumor necrosis factor; PDGF: platelet derived growth factor; FGF: fibroblast growth factor; IFN-γ: Interferon gamma; TNF-α: tumor necrosis factor alpha; NF-κB: nuclear factor κB

1. Introduction

The emergence of novel coronavirus strain SARS-COV-2 has resulted in the accumulation of critically ill patients in hospital beds across the globe. Our understanding of the nature of the infection has evolved dynamically and SARS-COV-2 infection which was perceived initially as pneumonia of unknown etiology is currently proven to cause derangement of immunological and endothelial physiology leading to prothrombotic tendencies and multiorgan dysfunction. The exponential trajectory of the spread of the infection coupled with increased morbidity and mortality have posed several unresolved clinical questions or dilemmas on the outcome of SARS-CoV-2 infection. Suspicions arise on lingering maladies in the patients who have recovered from COVID-19. Reports of restricted lung function and decreased exercise capacity were reported in long term survivors of SARS and MERS infections [1], the close allies of the causative virus of the current pandemic. At a stage, any virus can become a powerful stimulator of inflammation to such an extent that the inflammatory response gets stuck up in a sustained activated state even after the virus is eliminated. This review aims to identify the potential immune pathways that may lead to the development of chronic systemic inflammatory diseases post SARS-Cov-2 infection (Figure 1). Improved knowledge of the shared pathophysiology of COVID-19 and chronic immune diseases may help in devising diagnostic algorithms and therapeutic strategies to prevent or dampen the chronic complications of SARS-COV-2 infection in vulnerable patients.

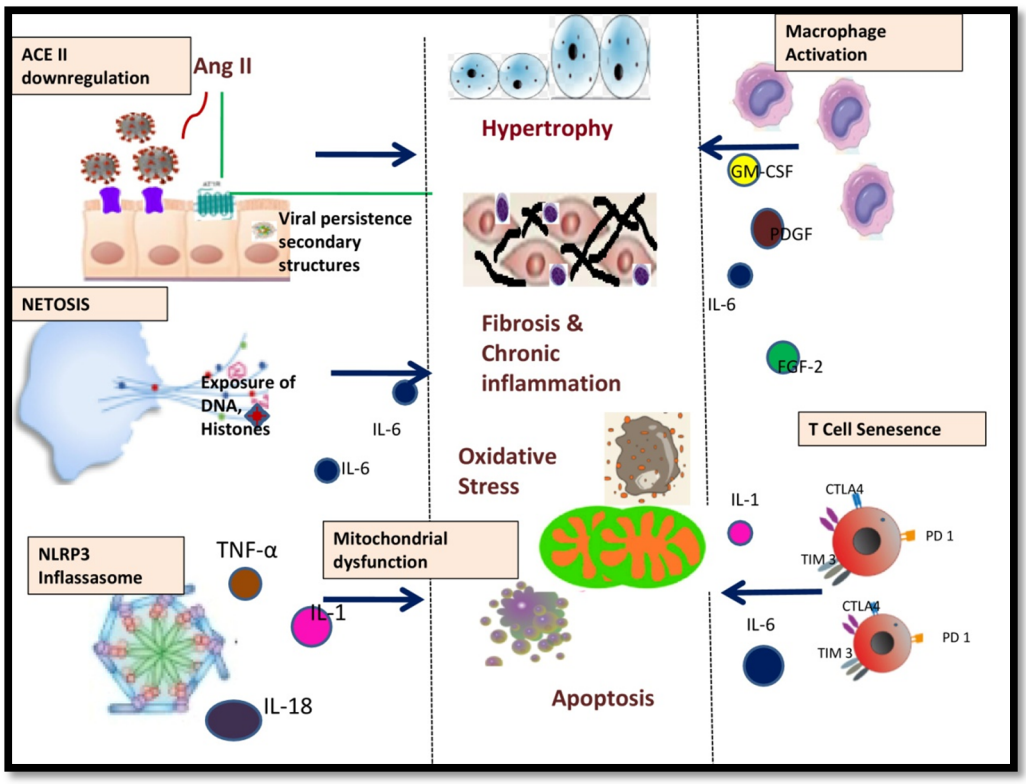

Figure 1. SARS-COV-2 induced immune pathways postulated to play a role in pathogenesis of chronic systemic inflammatory syndrome: Depicts the pathways common between immunopathogenesis of COVID-19 and chronic immune mediated inflammatory diseases.

2. Persistent antigenic stimulus and molecular mimicry

SARS-CoV-2 viral RNA is known to be present in various clinical samples for quite some time, and the durations reported in studies range from 33 days [2] to 82 days [3] from the onset of the symptoms. The genome of SARS-CoV-2 is known to be remarkably structured enabling shielding from host immunity. Presence of secondary structures throughout the viral RNA termed as "GORS" (genome ordered RNA structures) enable decreased viral recognition leading to defects in macrophage activation, T cell maturation and recruitment, thereby aiding viral persistence [4]. Molecular mimicry between viral proteins and host peptides may favor an aberrant activation of auto reactive T cells or B cells, leading to autoimmune response. Sharing of DAB1, SURF1, and AIFM peptides between the respiratory neurons in pre-Botzinger complex and SARS-CoV-2 viral proteins is hypothesized as a cause of respiratory failure in severe SARS-CoV-2 infected patients [5]. Viral proteins mimicking human peptides are also implicated in the pathogenesis of anemia, leucopenia, and vascular damage in COVID-19 patients [6].

3. ACE II downregulation

Binding of SARS-CoV-2 receptor binding domain to the host ACE II receptor [7] leads to internalization and shedding of ACE II. Downregulation of ACE II leads to a relative increase in Ang II tilting the RAS axis to the proinflammatory state. Ang II is believed to have pro-inflammatory, pro-oxidant, and pro-thrombotic, profibrotic properties [8] and interfere in intracellular insulin signaling. Elevated levels of angiotensin II are documented in liver fibrosis, pulmonary arterial hypertension, diabetes, obesity, and myocardial dysfunction. Increasing clinical evidence shows that the most common co-morbidities observed in COVID-19 patients, that are associated with worse prognosis and a higher rate of death, are systemic hypertension, diabetes, obesity, old age in which ACE II deficiency is known to be a significant determinant [9,10].

4. Dysregulated NLRP3 activation

Rapid and dysregulated NLRP3 activation by SARS-CoV-2 ion channel proteins E, and accessory proteins ORF 3a ORF 8b resulting in increased TNF-α, IL-1 and IL-18, is documented in SARS-CoV-2 infection [11]. Constitutive activation of NLRP3 inflammasome is associated with hereditary autoinflammatory diseases like familial cold urticaria syndrome (FCAS) [12], Muckle-Wells syndrome (MWS) [13], and chronic infantile neurological cutaneous and articular (CINCA) syndrome also known as neonatal onset multisystemic inflammatory disease (NOMID) [14].

5. Alternate macrophage activation

Pivotal role of macrophages in the pathogenesis of SARS-CoV-2 infection is demonstrated in many studies [15]. Lio et al. in a study on bronchoalveolar fluid demonstrated evidence of activation of M2 macrophages [16]. M2 macrophages possess a profibrotic profile and bring about vasculogenesis, cell proliferation. A microenvironment rich in M2 macrophages plays an important role in pulmonary fibrosis [17].

6. Neutrophil extracellular traps formation (NETosis)

Sera of severely ill COVID-19 patients show elevated NET breakdown products [18]. The intracellular components like DNA, MPO, histones externalized through NETosis have recognized autoantigens and defective clearing of these extruded components may prolong the half-life of the lattices leading to persistent inflammation and tissue damage [19]. Increased NET formation in blood and tissue lesions is reported in chronic diseases like ANCA antibody-associated vasculitis, rheumatoid arthritis, psoriasis, autoimmune pancreatitis, dermatomyositis, polymyositis, and multiple sclerosis.

7. Senescent activated secretory phenotype of T cells

T cells play a major role in viral clearance. In SARS-Cov-2 infection the number of T cells is reduced and the T cells are known to be in a senescent or functionally exhausted state, demonstrated by the expression of PD1, TIM-3 [20], and CTLA-4 and TIGIT. In the inflammatory milieu, the senescent cells are said to be in a hypo proliferative but functionally active state named as senescent activated secretory phenotype (SSAP). The SSAP cells are known to secrete many cytokines, growth factors, and proteases implicated in tissue injury [21]. T cell senescence is currently implicated in the pathogenesis of inflammatory bowel diseases and rheumatoid arthritis [22].

8. Interleukins

Elevated levels of IL-1β, IL-6, IL-7, IL-8, IL-9, IL-10, FGF, GM-CSF, IFN-γ, IL-10, MCP-1, PDGF, TNF-α, and VEGF are seen in COVID-19 patients compared to healthy adults. Table 1 discusses the relevant cytokines common between SARS-Cov-2 infection and chronic inflammation.

Table 1. Cytokines and their functions in relevance to both COVID-19 and immune-mediated inflammatory diseases.

Cytokine	Functions in chronic inflammation	Diseases associated
IL-1	Tissue destruction, fibroblast proliferation, collagen deposition, perpetuation of inflammation through IFN-γ, IL-17, GM-CSF	Alzheimer's diseases, amyotrophic lateral sclerosis, atherosclerosis, gout, rheumatoid arthritis
IL-6	Activates the endothelial cell, induction of IL-8, MCP-1, expression of adhesion molecules, transition from acute to chronic inflammation	Rheumatoid arthritis, systemic lupus erythematosis, psoriasis, Crohn's disease
FGF-2	Mitogen for fibroblasts, cell proliferation, migration, apoptosis of airway epithelial cells	Asthma, COPD, chronic bronchitis
GMCSF	Chemokine-17 induction and induction of fibroblasts and endothelial cells	Rheumatoid arthritis, Kawasaki disease, myocarditis
TNF-α	Cytotoxicity, cell growth, NF-κB activation	Rheumatoid arthritis, inflammatory bowel disease, Amyotrophic lateral sclerosis, Alzheimers disease
PDGF	Airway smooth muscle migration, fibroblast proliferation	Bronchial asthma, pulmonary fibrosis, pulmonary artery hypertension

9. Mitochondrial dysfunction

On evaluating ACE-II downregulation, NLRP3 inflassasome activation and inflammaging in the context of their close association with mitochondria, the distinct immune-metabolic pathways in SARS-Cov-2 infection, may be partially attributed to mitochondrial dysfunction. Mitochondrial molecules like mitofusin-2 [23] and Mitochondrial Antiviral Signaling Proteins MAVS [24] interact with NLRP3 during viral infections. Mitochondria act as scaffolds to NLRP3 inflassasome activation. Thompson et al. [25] identified unique population of $H3K27me3^{hi}VDAC1^{hi}$ T cells with upregulation of mitochondrial protein voltage dependant anion channel (VDAC1). $H3K27me3^{hi}VDAC1^{hi}$ T cells were associated with increased T cell apoptosis, and lacked traditional activation response to TCR stimulation. VDAC is a multifunctional mitochondrial membrane protein involved in release of mtDNA, inflassasome activation, apoptosis, type I Interferon release and is known to be a promoter of lupus like disease [26]. Increased VDAC3 is reported in SLE and VDACs are also reported to play a key role in neurodegenerative diseases, cardiac injury and neoplastic diseases [27]. Mitochondrial ROS and mtDNA release may have a role in initiation and upregulation of autoimmunity by promoting NETosis, cell survival disruption and induction of type 1 interferon signature [28]. Mitochondrial dysfunction is also associated with ageing, obesity, diabetes the comorbidities associated with severe COVID-19 [29]. Thus mitochondrial dysfunction may be a convergence point of multiple mechanisms driving increased inflammation and predisposition to autoimmunity in COVID-19 patients.

In line with the above discussions, there are definite intersections between the immune pathways of SARS-Cov-2 infection and immune-mediated inflammatory diseases at multiple levels. The outcome of the pandemic depends on the interaction between a genomic heterogeneous virus and an unpredictable immune system attributed to the mosaic global population with a variegated immune composition. The frenzied immune system may not shut off instantly but may linger in an activated state or resolve to scar the organs involved. Thus it is reasonable for us to hypothesize that COVID-19 may be the beginning of a new entity called a chronic viral systemic inflammatory syndrome.

10. Evaluation of the hypothesis

Multisystem dissemination of SARS-Cov-2 is possible because of ACE 2 expression on endothelial cells, smooth muscle cells, and perivascular pericytes in virtually all organs [30]. Autopsy studies show macrophage infiltration, peri-bronchial fibrometaplasia, thickened alveolar walls, and fibrous proliferation in the lung parenchyma. Reports on possible chronic sequelae of SARS-CoV-2 infections are surfacing recently. Figure 2 summarises the major chronic effects reported and the postulated underlying mechanisms. Combet et al. reported aggressive pulmonary fibrosis in a patient who recovered from the acute infection without mechanical ventilation [31]. Myocyte degeneration with interstitial hyperplasia and CD20 positive lymphocytic infiltrates were also seen in the myocardium. A Kawasaki disease like presentation with a higher rate of cardiac involvement and macrophage activation termed, multisystem inflammatory syndrome (MIS-C), is reported in children with evidence of COVID antibodies in the serum [32]. In a study on German patients cured of COVID-19, 60% had persistent ongoing inflammation in the myocardium and pericardium, irrespective of the severity of the clinical presentation in the acute infection [33].

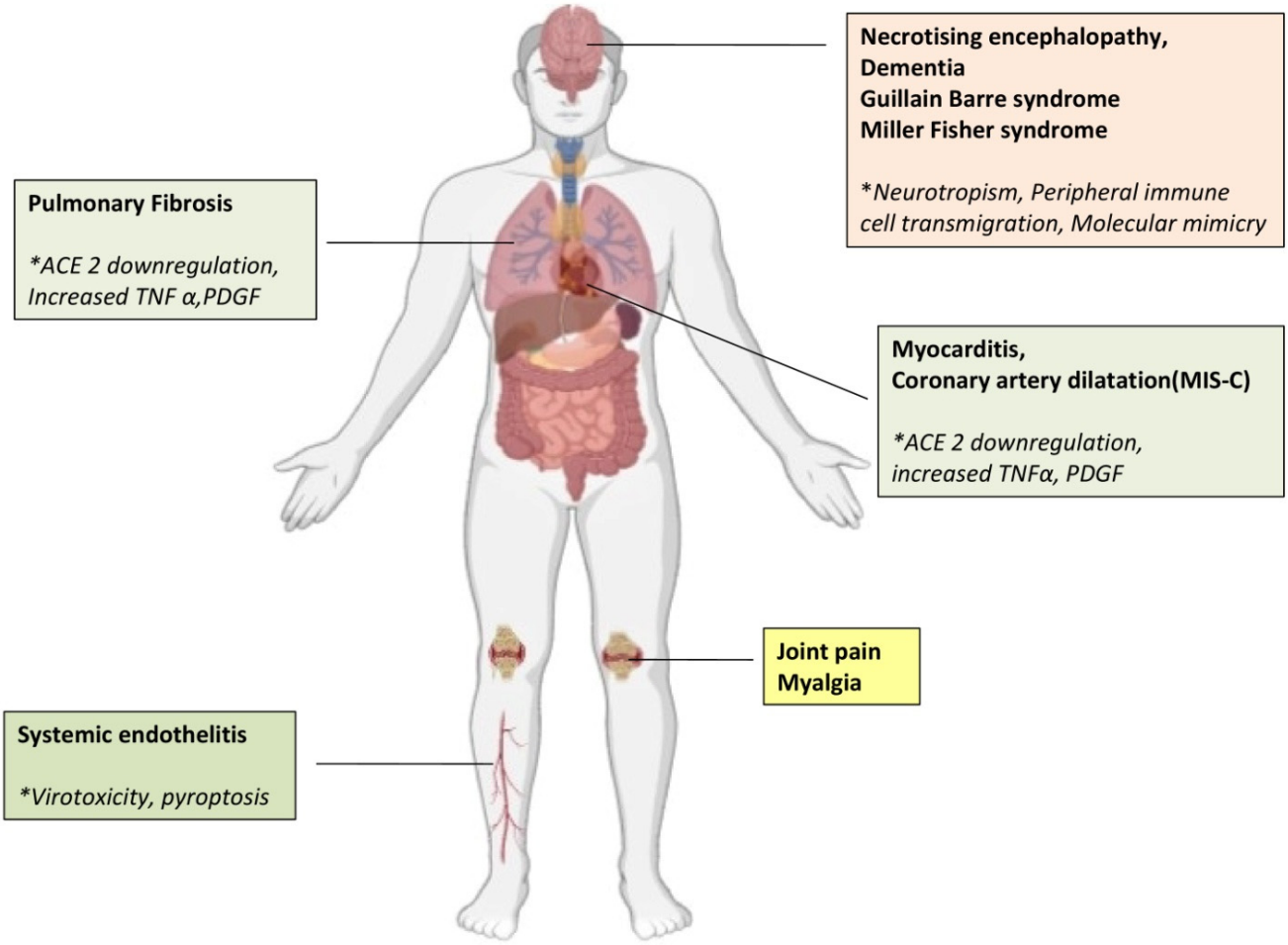

Figure 2. Chronic sequelae reported in COVID 19 survivors and the proposed underlying mechanisms: Depicts the major post COVID chronic sequelae reported and the underlying mechanisms proposed.

11. Conclusions

As of now owing to the remarkably high proportion of the global population affected, only the acute effects of the pandemic are coming to light. It will take a few years to determine the chronic effects of SARS-CoV-2 infection. The breadth of the current SARS-Cov-2 pandemic may require a closer examination of the underlying mechanisms, preventive measures, diagnostic methods, and interventions for post-viral systemic chronic inflammatory sequelae. Thus follow-up of COVID-19 survivors is indispensable to fully appreciate and mitigate a deleterious pile-up of patients with chronic diseases precipitated by the pandemic.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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