UDC 578.24 doi: https://doi.org/10.15407/ubj93.01.018

A VICIOUS CIRCLE BETWEEN OXIDATIVE STRESS AND CYTOKINE STORM IN ACUTE RESPIRATORY DISTRESS SYNDROME PATHOGENESIS AT COVID-19 INFECTION

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Received: 31 August 2020; **Accepted:** 17 December 2020

In early December 2019, the pandemic of coronavirus disease 2019 (COVID-19) began in Wuhan City, Hubei Province, China. Since then, it has propagated rapidly and turned into a major global crisis due to the high virus spreading. Acute respiratory distress syndrome (ARDS) is considered as a defining cause of the death cases. Cytokine storm and oxidative stress are the main players of ARDS development during respiratory virus infections. In this review, we discussed molecular mechanisms of a fatal vicious circle between oxidative stress and cytokine storm during COVID-19 infection. We also described how aging can inflame the vicious circle.

K e y w o r d s: acute respiratory distress syndrome (ARDS), COVID-19, cytokine storm, oxidative stress.

For years, it has been predicted that human coronavirus (HCoVs) can become a global public health threat [1]. With the emergence of novel CoVs in December 2019 in Wuhan, China, the prophecy turned into a tragedy. The global outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. Acute respiratory distress syndrome (ARDS) is considered as more classic symptom and the most significant complication of COVID-19 patients who come to the hospital [3]. ARDS is a type of respiratory disorder that is characterized by stiff and inflamed lung, shortness of breath, cough, as well as breathing difficulties [4]. Additionally, COVID-19 infection is associated with long term complications (such as neurodegenerative disease) in patients who survived. It is reported that the mortality of COVID-19 is 35-50% [4, 5]. Because of COVID-19 global outbreak and its economic and social impact, exploring mechanism and therapeutic targets of ARDS seem to be a necessity. The management of ARDS is challenging because of its multifactorial and complex pathogenesis [6]. Several evidences reported that the imbalance between oxidant and antioxidant capacity or oxidative stress plays a major role in the development of ARDS in respiratory diseases [7].

Reactive oxygen species (ROS) are a defense system during virus respiratory infections [8]. Various cell types in the lung can produce ROS, including monocytes and macrophages, neutrophil, as well as the pulmonary endothelial and epithelial cells [7]. These cells express the ROS-generating enzyme such as nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidases, Nox) and Xanthine oxidase (XO) [7, 8]. In physiological

condition, endogenous antioxidants such as superoxide dismutase (SOD) neutralize free radicals and also their harmful effect [9]. However, these antioxidants are rapidly overwhelmed during some pathological conditions, leading to excess level of ROS and subsequent cell injury by various mechanisms including; direct damage, lipid peroxidation, oxidation of proteins leading to release of proteases and inactivation of antioxidant and antiprotease enzymes and alteration of transcription factors such as activator protein-1 (AP-1) and nuclear factor (NF)-KB, leading to enhanced expression of proinflammatory cytokine (cytokine storm) which is associated with the pathogenesis of ARDS during virus respiratory infections [9-11]. Proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) can stimulate the formation of ROS, worsening ARDS and lung injury [12]. Indeed, likely there is a vicious circle between oxidative stress and cytokine storm in ARDS pathogenesis. Hence, pathological conditions, which are associated with the overproduction of ROS can inflame the vicious circle.

Aging is an intricate process with classic hallmarks, including genomic instability, telomere attrition, mitochondrial dysfunction and cellular senescence. It is well accepted that oxidative stress plays a central role in the aging related disease [13]. Therefore, aging can potentiate the ARDS development in respiratory viral infections [14].

In the present review, we discussed the molecular mechanism behind redox biology of SARS-CoV2 as a respiratory virus. We focus on how cytokine production following oxidative stress lead to ARDS as the leading cause of mortality. The intersections of oxidative stress and aging have been also described. Finally, we review long term effects of COVID-19 infection in patients that recovered.

Mechanism of enhanced ROS production during COVID-19 infection

Excess ROS production and reduced levels of antioxidant enzymes are outstanding features of respiratory viruses [15, 16]. Some sources of ROS production during SARS-CoV2 infection in host cells are summarized below.

NOX2 as main source of ROS in respiratory viruses

Nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidases, Nox) is one of the main sources of ROS production during physiological and pathophysiological conditions [17, 18]. NOX is considered as a professional ROS producer [7]. Five different NOX isoforms have been identified: NOX1, NOX2, NOX3, NOX4, NOX5 (22, 23). NADPH oxidase 2 (NOX2) is a multicomponent enzyme with two membranes bound subunits (gp91phox, p22 phox) and three cytosolic subunits (p67 phox, p47 phox, and p40 phox). In addition to these subunits, small GTPase Rac1 or Rac2 may be associated with NAPDH oxidase [18]. The contribution of NOX2 in respiratory viruses-induced ROS production has been confirmed [19-23]. NOX2 is a phagocytic enzyme, which is expressed in monocytes, neutrophils macrophages, as well as on air way epithelial cells [24]. It is reported that NOX2 oxidase plays a pivotal role in the killing of bacteria and fungi through phagosomal ROS production. However, NOX2 oxidase does not appear to eliminate viruses in a manner analogous to that for bacteria. In fact, in the absence of NOX2 oxidase, influenza A virus causes substantially less lung injury, and viral burden, suggesting that NOX2 oxidase-derived ROS promotes rather than inhibits viral infection [21, 25]. It is identified that p47phox phosphorylation has critical role in the activation of NOX2 [18]. Different signaling pathways involved in the initiation of p47phox phosphorylation [18]. Several lines of evidences revealed that in endothelial cells, TNFα stimulates PKCzeta which subsequently phosphorylates p47phox, NOX2 assembly and ROS production [26, 27]. In polymorphonuclear leukocytes (PMN), TNFα can activate NOX2 signaling through different mechanisms [28].

NOX2-dependent ROS production is also activated by the family of toll-like receptors (TLRs) [29]. It is reported that TLRs are a class of pattern recognition receptors (PRRs) that initiate the innate immune response through the recognition of pathogen-associated molecular patterns (PAMPs). TLR7 belongs to a class of PRRs which recognizes single strand RNA (ssRNA) of pathogen [30]. SARS-CoV-2, a single-stranded-RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. The COVID-19 particles bind to the receptor-binding motif in the receptor binding domain (RBD) [31]. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells [32]. After entry into cells, ssRNA binds to TLR7. The TLR7 signaling induces p47phox phosphorylation and subsequent

NOX2 activation and ROS production [33]. In addition, TLR7 signaling via the adaptor myeloid differentiation primary response protein 88 (MYD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF) results in the activation of several transcriptional factor including; nuclear factor-κB (NF-κB), IFN- regulatory factor 7 (IRF7) and mitogen activated protein kinase (MAPK). All of these factors can highly increase pro-inflammatory cytokines production [30] (Fig. 1).

Mitochondrial ROS production during SARS-COV2 infection

Mitochondria are the major resource of ROS in the mammalian cell types. Mitochondria produce ROS predominately at the electron transport chain (ETC) complex I and complex III during oxidative phosphorylation (OXPHOS) [34]. Invading pathogen triggers alterations in cellular metabolism and mitochondrial function resulting in increased mitochondrial ROS (mtROS) production, which is associated with mitochondrial DNA (mtDNA) damages and apoptosis [35]. In addition to apoptosis, mtROS can stimulate innate immune responses during bacterial and viral infections [36, 37].

To the best of our knowledge, there is no direct evidence indicating the production of mtROS during SARS-CoV2 infection. Nevertheless, there is some indirect evidence that SARS-CoV infection triggers ROS production and apoptosis through the mitochondrial pathway. SARS-CoV nucleocapsid protein induces mitochondrial dysfunction resulting in mtROS overproduction and apoptosis in COS-1 cell [38]. It is revealed that the 3C-like protease (3CLpro) of SARS-CoV can increase ROS production, which leads to apoptosis in HL-CZ cells [39]. The involvement of other SARS-CoV proteins such as M, E, S, ORF-6, 7a and 9b in apoptosis, which could be

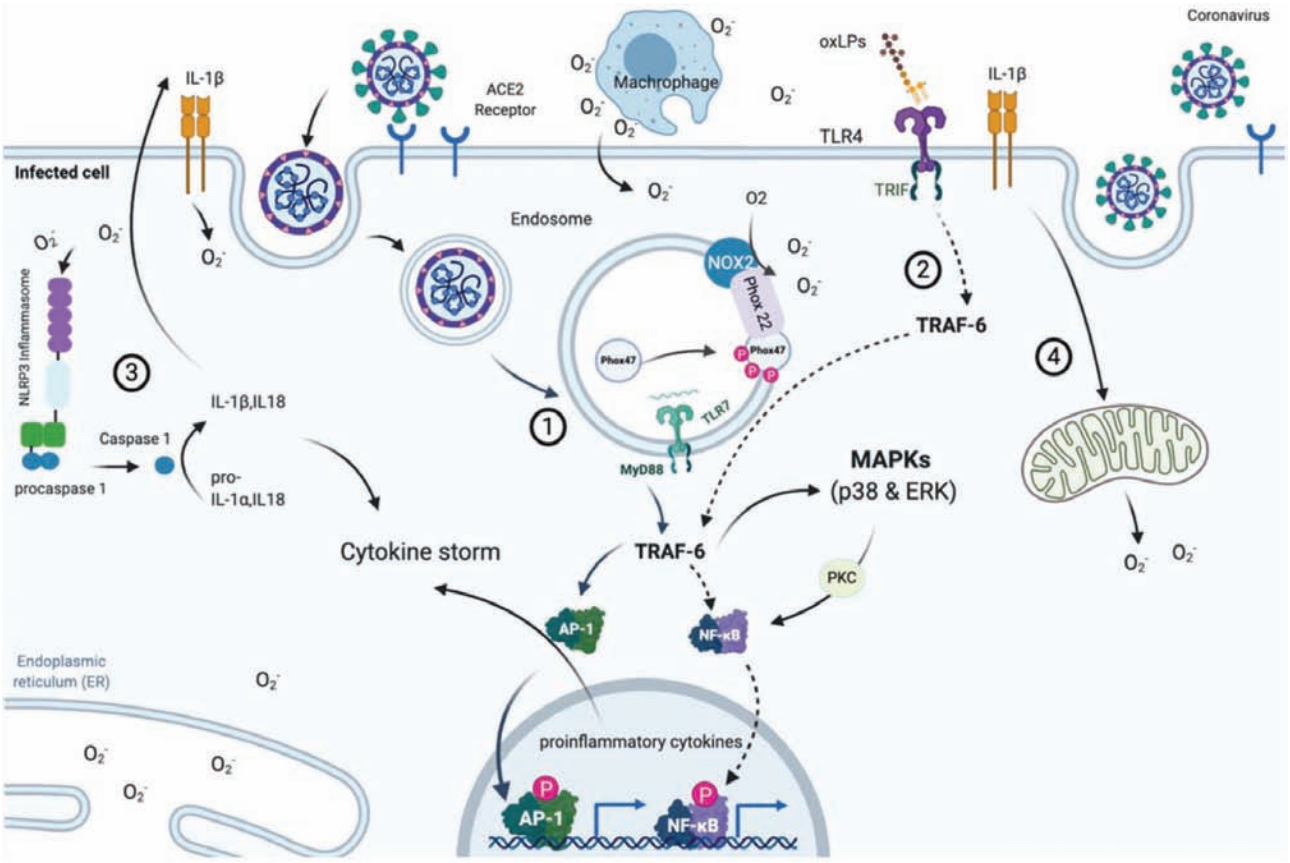

Fig. 1. Schematic shows: (1) SARS-CoV infection can induce ROS production and proinflammatory cytokines and MAPK kinase can amplify cytokine production. (2) Oxidative stress can potentiate proinflammatory cytokines production through TLR4 signaling pathway. (3) Oxidative stress active inflammasome which lead to production of IL-1ß and IL-18. (4) IL-B signaling pathway causes mitochondrial dysfunction and ROS production. Created with BioRender.com

associated with the mtROS production, have been studied [40, 41].

Endoplasmic reticulum stress can be a source of ROS production during SARS-COV2 infection

HcoVs, as intracellular obligate parasites, induce endoplasmic reticulum stress (ER Stress) or unfolded protein response (UPR) as a result of overloading of protein synthesis and processing during viral infection [42]. ER stress is regulated by various signaling pathways, which are initiated by three receptors in ER membrane: 1) activating transcriptional factor 6 (ATF6), 2) inositol-requiring protein 1 (IRE1), and 3) protein-kinase-R (PKR)-like endoplasmic reticulum kinase (PERK). Over production of ROS is not only as an integral component, but also as a consequence of ER stress. Different mechanisms have been defined for production of ROS under ER stress, which have been mentioned above [43]. Activation of ER stress has been studied during SARS-CoV infection. The S and 3a proteins of SARS-CoV can activate the PERK signaling [44, 45]. Accessory proteins of SARS-CoV, which are located in luminal surface of the ER surface, can activate the ATF6 signaling [46]. The role of IRE1 pathway has been also reported during SARS-CoV infection. The E protein of SARS-CoV can inhibit IRE1 signaling pathway [47].

ROS-mediated cellular signaling induces cytokine storm during SARS-CoV2 infection

It is reported that cell signaling proteins can be affected by ROS overproduction [48]. Changes in cell signaling proteins always associated with pathological conditions such as overproduction of proinflammatory cytokines, which is named cytokine storm [7, 48]. In the following section, we discuss ROS-activated signaling pathways that involving in the cytokine storm and subsequent lung injury during SARS-CoV2 infection.

ROS and NFκB signaling pathway

The NFκB is considered as a ROS dependent transcription factor, which plays a pivotal role in the activation of the innate immune system [48, 49]. ROS-dependent activation of NF-κB triggers massive production of proinflammatory cytokines and chemokines, such as TNFα, IL-1, IL6, and IL8 [49]. The NF-κB also plays a major role in pathogenesis of most infections, including those caused by viruses. Accordingly, NF-κB has been considered as a potential therapeutic target in microbial diseases [50].

The role of NF-κB activation in pathogenesis of SARS-CoV has been also studied. SARS-CoV proteins E, spike, nucleocapsid and nonstructural proteins (nsps) promote NF-κB activation [51-56]. Studies have been shown that absence of these proteins, resulting in attenuated lung injury because of a decrease in proinflammatory cytokines and reduction in the neutrophils infiltration in lung tissue [51].

ROS and MAPKs signaling pathway

The mitogen-activated protein kinases (MAPKs) are a group of protein kinases which are activated in response to a variety of environmental stimulators including oxidative stress, viral infection and proinflammatory cytokines [57]. The MAPK signaling pathways have been classified into three main groups, including the extracellular signal-related kinases (ERKs), the c-Jun N-terminal kinases (JNKs), and the p38 kinase (p38) pathways [58]. Activation of MAPKs signaling proteins has been detected during SARS-CoV infection, which can potentiate the ROS-activated MAKPs cascade. The proteins of SARS-CoV such as S and 3b proteins can stimulate upregulation of proinflammatory cytokines through ERK/AP1 signaling pathway activation [59, 60]. The S protein of SARS-CoV can activate the ERK/NF-κB pathway via activation of PKC alpha [61]. Involvement of other SARS-CoV proteins such as 3b, 3a, 7a in the JNK activation and increased cytokines production has also been reported [53, 60]. Increased level of IL-8 as a result of P38 MAPK activation has been detected during SARS -CoV infection [62].

ROS and TLR4 signaling pathway

During SARS-CoV infection, oxidized phospholipids (OxPLs), as a product of oxidative stress, can trigger the activation of TLR4 and subsequently NF-κB [15]. It is identified that both of the TIR-domain-containing adapter-inducing interferon-β (TRIF) and TNF receptor associated factor 6 (TRAF6) mediate activation of NF-κB, as adaptor molecules. Therefore, TLR4-TRIF-TRAF6-NF-kB signaling pathway resulting in overproduction of proinflammatory cytokines, leading cytokine storm. Cytokine storm together with excess ROS production can worse lung injury and ARDS in COVID-19 infection [15, 63].

ROS activate inflammasome complex

The NLRP3 inflammasome is activated through a ROS dependent pathway in the respiratory viruses [19, 64]. Inflammasomes are multiprotein complexes consisting of an intracellular sensor such as nod-like receptor proteins (NLRPs), the adaptor apoptosis-associated speck-like protein containing a carboxy-terminal CARD (i.e.ASC) and procaspase1 [65]. The NLRP3 is a well characterized NLR sensor molecule, which is activated by NOX2-mediated ROS or mitochondrial ROS during respiratory virus infections [64]. It has been also shown that ROS activates inflammasome-activating signal transduction pathways via the phosphatidylinositol-3-kinase (PI3K) and MAPK signaling pathways. As a component of the innate immune system, activation of inflammasome complex results in proteolytic processing of pro-caspase 1 into activated caspase 1, which in turn causes proteolysis of pro-IL-1β and pro-IL-18 (in active form) into IL-1β and IL-18 (active form), respectively [65].

In addition to ROS dependent pathway, NLRP3 inflammasome activates through ROS-independent pathway. Shi et al. (2019) showed the role of ORF8b protein in activation of NLRP3 inflammasome during SARS-CoV infection. Mechanistically, ORF8b interacts directly with the leucine rich repeat (LRR) domain of NLRP3 and triggers robust NLRP3 inflammasome activation and IL-1β release [66]. Disturbance of calcium homeostasis can stimulate inflammasome activation during coronavirus infection. The E protein of SARS-CoV, which comprises only 76 amino acids, forms Ca^{2+} permeable ion channels and activates the NLRP3 inflammasome [67]. SARS-CoV 3a viroporin with ion channel activity also activates the NLRP3 inflammasome [68]. Improper regulation of inflammasome production could adversely affect the balance between pro- and anti-inflammatory cytokines, cytokine storm, leading to inflammation. The NLRP3 Inflammasome also promotes oxidative DNA damage. Both of the inflammation and DNA damage lead to an inflammatory form of programmed cell death, named pyroptosis. Subsequently, pyroptosis can further release ROS from damaged cells. So, all of these events causes small vicious cycle between inflammasome and ROS production lead to further tissue injury [65].

ROS and Nrf2 signaling pathway

Nuclear factor E2-related factor 2 (Nrf2) signaling pathway plays a main role in keeping the balance of the cellular redox statue to prevent oxidative stress [69]. The Nrf2 signaling is activated by the increased level of intracellular ROS through different mechanisms. The Nrf2 signaling can trigger the expression of antioxidant enzyme such as superoxide dismutases (SOD), catalase (CAT), peroxiredoxins, and glutathione peroxidases (GPx) [70]. Furthermore, Nrf2 can inactivate NF-κB pathway, then control cytokine overproduction. Indeed, there is a crosstalk between NF-κB and Nrf2 signaling pathways, in which negatively regulate each other to maintain redox homeostasis in physiological condition [71]. However, in pathological condition this regulation is disturbed, resulting in oxidative stress and inflammation leading to tissue injury. Reinforcement of NF-κB or suppression of Nrf2 by the other signaling pathways causing imbalance in Nrf2–NF-κB regulation [72, 73]. Therefore, it seems that simultaneous targeting NF-κB and Nrf2 signaling using pharmacological agents can be a promising therapeutic strategy for inflammatory disease such as ARDS.

The role of Nrf2 in the respiratory virus pathogenesis is controversial [8, 74]. Unlike non- pathogenic Influenza virus (IV) strains, in highly pathogenic IV strains, phosphorylated form of Nrf2 is not imported to the nucleus [75]. This discrepancy could be justified with dysregulated Nrf2-NF-κB crosstalk. Although, there is not clear information about Nrf2-NF-κB signaling pathway in the SARS-CoV infection. It is reported that transient activation of Nrf2 during the early stage of viral infection may be related to dysregulation of Nrf2-NF-κB signaling pathway. Some evidence reported activation of NF-κB by SARS-CoV proteins [53-56] and inhibition of Nrf2 by ROS-activated MAPK/ERK pathway [71] (Fig. 2).

Proinflammatory cytokines can trigger ROS production

There is a positive feedback loop between ROS generation and cytokines produced by NF-kB signaling pathway [48]. TNFα is one of the main proinflammatory factors which are secreted in response to SARA-CoV-2 infection [76]. TNF could trigger

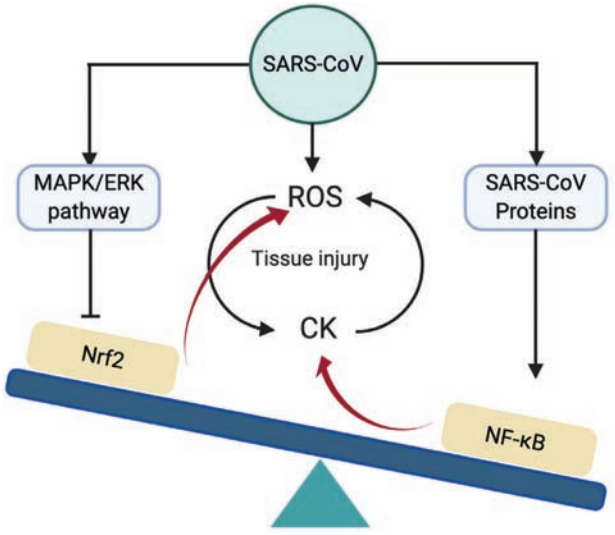

Fig. 2. The diagram shows how SARS-CoV infection can induce dysregulated Nrf2-NF-κB cross-talk leads to a viscous circle between ROS production and proinflammatory cytokine. Created with BioRender.com

ROS production, though mitochondrial and NOX pathways [77]. TNFα induces caspase-8 activation, which alters mitochondrial function, increases ROS production [12]. Engagement of TNF and TNF receptor1 (TNFR1) leads to NOX complex activation [78]. IL-1β also can elevate the cellular ROS level through reduction of mitochondrial complex1 [79]. Increase in ROS production in response to TNF-α, and IFN-γ has been also reported by yang and coworkers [77].

Delayed IFN-I signaling can potentiate the fatal vicious circle during SARS-CoV2 infection

Type I interferons (IFN-I) are secreted by infected cells and induce innate and adaptive immune responses via Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway, leading to expression of IFN-stimulated genes (ISGs) which their products initiate an intracellular antimicrobial programmed that limits the spread of infectious agents, especially viral pathogen [80]. Type I interferons responses keep the balance between activating and suppressive signals to prevent hyperinflammation. The final outcome of IFNs signaling is influenced by host, pathogen and environmental factors. Imbalance of IFN-I responses resulting in hyper-inflammation [81].

Studies have been shown that SARS-CoV infection is accompanied by a delayed IFN-I signaling which lead to enrollment of monocytes into the lungs as a result of the enhanced release of monocyte chemoattractants by alveolar epithelial cells. Continued recruitment of blood monocytes into the lungs resulting in accumulation of pathogenic inflammatory monocyte-macrophages (IMM), which leads to hyper-inflammation and impaired virus-specific T cell responses [82]. The CoV-specific T cells play an important role in virus clearance and limit lung injury. Therefore, impaired T cell responses causing hyper-inflammation, cytokine storm, and excess ROS production during SARS-CoV infection [83]. The ORF-9b protein of the SARS-CoV localizes to host mitochondrial outer membrane. It can trigger degradation of mitochondrial-associated adaptor molecule MAVS as adaptor molecules in type I IFN signaling pathway. In this way, SARS-CoV escapes innate immune responses [84]. Coronavirus 3a protein induces PERK activation resulting in suppression of IFN1 signaling and innate immunity. The 3a protein inhibits IFN1 signaling via induction of IFN alpha-receptor subunit 1 (IFNAR1) degradation [44]. Coronavirus papain-like protease (PLpro) is a deubiquitinating enzyme which works as a type I IFN antagonist. Plpro downregulate ERK1 pathway and suppress IFN-α-induced responses [85].

Age-associated changes are in favor of the fatal vicious circle during SARS-CoV2 infection

Inflammaging, a chronic state of inflammation, is associated with the over-production of ROS and hyper-inflammation in the elderly population. Inflammaging predispose age-associated disease such as respiratory and infectious diseases [86]. It seems that inflammaging increased fatal vicious circle during SARS-CoV2 infection.

Several mechanisms can be proposed for hyper-inflammation in the aging. The declining T cell function is the most significant age-associated changes of immune cells [87]. In old macrophages, increased production of prostaglandin E2 (PGE2) as T cell-suppressive factor results in up-regulation of NF-κB. Subsequently, up-regulation of NF-κB leading to over-production of proinflammatory cytokines [87]. Reduced expression of growth factor independence-1 (Gfi-1) and increased expression of suppressors of cytokine signaling 3 (SOCS3) have been reported in older mice compare to young

mice [88]. Macrophage migratory inhibitory factor (MIF) is one of the master regulators of senescence-associated immune response [14]. The MIF, as a proinflammatory cytokine, promotes macrophages to release cytokines and produce ROS [89, 90]. Although, the role of MIF has not been studied in the pathogenesis of SARS-CoV, but its role in the pathogenesis of some respiratory viruses such as H5N1, influenza A and RSV has been characterized [91]. The MIF activate macrophage to release proinflammatory cytokines such as MCP-1, IL-10 and TNF. It also induces NADPH oxidase-derived ROS generation [91]. The second dimension of inflammaging is age-associated ROS overproduction. Oxidative stress is a hallmark of the aging process. Aging is associated with overproduction of ROS and deprivation of the antioxidant system. During the aging process, mitochondrial dysfunction and dysregulated Nox activation are attributed to ROS overproduction [92]. Taken together, there is a vicious cycle between ROS and cytokine production, which is the main cause of lung injury and ARDS during respiratory virus infection. Although, lung injury and ARDS are the important cause of admission of COVID-19 patients in the hospital. However, several studies reported the COVID-19 infection can induce several neurologic diseases in patients who recover. In the next section, we review the long-term side effects of COVID-19 particles in patients who recover.

The long-term complication of COVID-19 infection on central nervous system

Butlera and Barrientosa in 2020 reported that systemic inflammation caused by COVID-19 particles may have long-term side effects in patients that recover, including dementia and neurodegenerative disease [93]. Moreover, several evidences reported the incidence of Kawasaki-like disease in the children with COVID-19 infection [94]. Additionally, Verdoni and colleagues in 2020 reported that incidence of Kawasaki-like disease 30-fold increased quickly after the spread of COVID-19 infection to Bergamo-Italy [95]. Kawasaki disease is an inflammatory vascular disease that mostly involves children under 5 years old [94]. TNF-α plays an important contribution in aneurysmal formation of coronary arteries in Kawasaki disease [96]. It is also suggested that COVID-19 infection can increase inflammaging related disease, including neurodegenerative disorders, even in younger individuals [96]. The underlying mechanism of neural complication of COVID-19 in patients is far from clear. In one hand, COVID-19 particles can directly changes blood-brain barrier properties in human, leading to an additional mechanism of entry to central nervous system [97]. In addition to COVID-19 particles, it is also well accepted that SARS-CoV and MERS-CoV particles have neuro-invasive properties [98]. It is reported that SARS-CoV particles were observed in neurons and brain samples from patients diagnosed with SARS [99]. In other hand, excess production of pro-inflammatory markers during COVID-19 (cytokine storm) indirectly can induce long-term side effects in patients that recover [93, 94]. Additionally, it is identified that ACE2 express in both neurons and glia, suggesting the brain may be a potential target of COVID-19 particles [98]. Since neuroinflammation can be induced or worsened by both stress and COVID-19 infection. So, the contribution of neuroinflammatory mechanisms could be central in a vicious circle leading to an increase in the mortality risk in elderly adults with COVID-19 infection. Additionally, neuroinflammation and subsequently neurodegenerative disease can be important long-term side effects of COVID-19 [100].

Proinflammatory cytokines and ROS production are hallmarks of innate immunity during SARS-CoV2 infection. Molecular mechanism indicates that the development of vicious cycle between ROS and cytokine is the main cause of lung injury and ARDS during respiratory virus infection. Additionally, this vicious cycle can induce several neurological diseases in the patients who recover from COCID-19 infection such as neurodegenerative disease. Targeting this vicious circle can be a promising therapy against lung injury and ARDS development during SARS-CoV2 infection.

Acknowledgment. This article was supported by Biochemistry and Physiology department of Baqiyatallah University of Medical Sciences (BMSU).

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. This work was supported by Department of Biochemistry of BMSU and the authors.

ЗАМКНЕНЕ КОЛО МІЖ ОКСИДАТИВНИМ СТРЕСОМ ТА ЦИТОКІНОВИМ ШТОРМОМ У ПАТОГЕНЕЗІ ГОСТРОГО РЕСПІРАТОРНОГО ДИСТРЕС-СИНДРОМУ ЗА ЗАРАЖЕННЯ COVID-19

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На початку грудня 2019 року в місті Ухань провінції Хубей (Китай) розпочався спалах коронавірусної хвороби 2019 (COVID-19). З того часу пандемія значно поширилась і перетворилась на велику світову кризу через швидке розповсюдження коронавірусу. Основною причиною летальності вважають гострий респіраторний дистрес-синдром (ARDS – acute respiratory distress syndrome) – синдром гострої дихальної недостатності. Цитокіновий шторм та оксидативний стрес є основними гравцями за розвитку ARDS під час респіраторних вірусних інфекцій. У цьому огляді обговорено молекулярні механізми формування фатального замкненого кола між оксидативним стресом та цитокіновим штормом у разі зараження COVID-19 та описано чому старіння може сприяти виникненню такого кола.

Ключові слова: ARDS, COVID-19, цитокіновий шторм, оксидативний стрес.

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