Genbinesia 2 (3): 123 – 129 (2023)
doi: https://doi.org/10.55655/genbinesia.v2i3.39
http://journal.genbinesia.or.id/

RESEARCH ARTICLE

GENBINESIA Journal of Biology

DNA damage, inflammation, and cellular senescence investigation in SARS-CoV-2 infection: A short review

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Received:
15 May 2023
Accepted:
20 June 2023
Published:
31 July 2023

Abstract

SARS-2 infection is predicted to trigger DNA damage due to excessive inflammatory responses from the immune system such as cytokine storms. The cytokine storm leads to an increase oxidative stress in cells, possibly triggering senescence through activation of the DDR signalling pathway. Alterations in the DDR pathway that induce cellular senescence have been identified due to the regulation of viral proteins that lead to impaired DNA repair. However, previous studies have not examined the relationship between DNA damage, inflammation, and cellular senescence. In this short review, we will discuss with a simple perspective why SARS-CoV-2 infection can accelerate the cellular senescence process and its relationship with the inflammatory response.

Keywords: COVID-19, Cytokine storm, DNA damage response, Inflammation, Senescence

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the main cause of the coronavirus-19 (COVID-19) outbreak, can be spread through droplets from an infected person[1]. When the viruses enter the body, they will spread to the respiratory tract and reach cells in the lungs. SARS-CoV-2 initiates infection by binding to the angiotensin converting enzyme-2 (ACE-2) receptor to trigger endocytosis and fusion into host cells[2]. Infected cells will respond with pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-18 (IL-18). SARS-CoV-2 can

trigger disruption of the regulation of pro-inflammatory cytokine secretion in host cells through an excessive increase in a secretion that causes a cytokine storm[3,4]. Cytokine storm is the failure of the body's immune response to tackle SARS-CoV-2 infection due to an excessive inflammatory response caused by the influence of several viral proteins. The regulation of pro-inflammatory cytokines is affected by the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This factor is reported to be increased in the body of COVID-19 patients who suffered a cytokine storm[5]. Furthermore, the cytokine storm is caused by disruptions in the signaling regulation of the DDR pathway in host cells in addition to the massive release of pro- inflammatory cytokines[6].

Deoxyribonucleic acid damage response (DDR) is a cellular biological pathway that plays a role in defense mechanisms, repair, and cell death program. If genetic damage to cells cannot be repaired through DDR, activation of apoptotic signaling will be occured[7]. DDR is also activated when SARS-CoV-2 virus infection occurs but there is a failure of regulation[8]. This is triggered by the integration of the SARS-CoV-2 genome in host cells and the activity of viral proteins. Disruption of the DDR signaling pathway when cells are infected with SARS-CoV-2 can trigger apoptotic failure, genetic damage, cell senescence, and cytokine storm phenomena[9]. SARS-CoV-2 infection can trigger cellular senescence as the virus causes DNA damage and triggers chronic inflammation that results in increased oxidative stress in cells[10]. The virus can trigger the activation of DDR resulting in increased production of pro-inflammatory cytokines. However, previous studies have not revealed a clear mechanism of the relationship between DDR and accelerated senescence during SARS-CoV-2 infection.

Why does SARS-CoV-2 infection enable accelerated senescence?

DDRs consist of deoxyribonucleic Acid (DNA) repair mechanisms, the ability to adapt or tolerate damage, and cell-cycle checkpoints regulation[11,12]. Some DNA repairs mechanisms such as the activity of a photolyase that can repair DNA damage caused by ultraviolet (UV) light and the suicide enzyme O6-methylguanine transferase (MGMT) trigger the displacement of methyl groups from DNA by forming covalent bond interactions[13,14]. Failure or disruption of the DDR response can trigger diseases such as autoimmunity, cancer, early senescence, and the severity of viral infections[15,16]. Previous studies have shown the disruption of DDRs due to viral infections such as host cells entering S phase inappropriately due to the virus triggering DDRs by altering signalling pathways through various viral accessory proteins[17]. However, the DDR signalling pathways that are disrupted by viral accessory proteins appear to be less explored.

Ribonucleic acid (RNA) viruses such as SARS-CoV-2 are the trigger of the 2019 pandemic or COVID-19[18]. The virus has a genome length of about 30 kb consisting of 26 polypeptides with 16 non-structural proteins (NSPs)[19]. Structural proteins consist of nucleocapsid (N), spike (S), envelope (E), and membrane (M)[20–22]. Viral infection can affect several biological pathways in cells such as DDR and ubiquitin-proteasome system (UPS), both of which are rarely known in the life cycle of RNA viruses[23]. The relationship between SARS-CoV-2 infection and interactions with several proteins involved in DDR is still lacking information. The DDR pathway plays an important role in signalling the coordination of DNA repair. Single and double chain breaks in DNA are performed by a protein such as replication A (RPA) and MRE11-RAD50-NBS1 (MRN) complex which has an important role in the initial processing of DNA strand breaks before the repair process takes place[24]. Both can recruit two factors to phosphorylate

and autophosphorylate several other DDR factor kinases such as checkpoint kinase 1 and 2 (CHK-1,-2). Activation of the DDR pathway can trigger inflammation, senescence, and cell death[25].

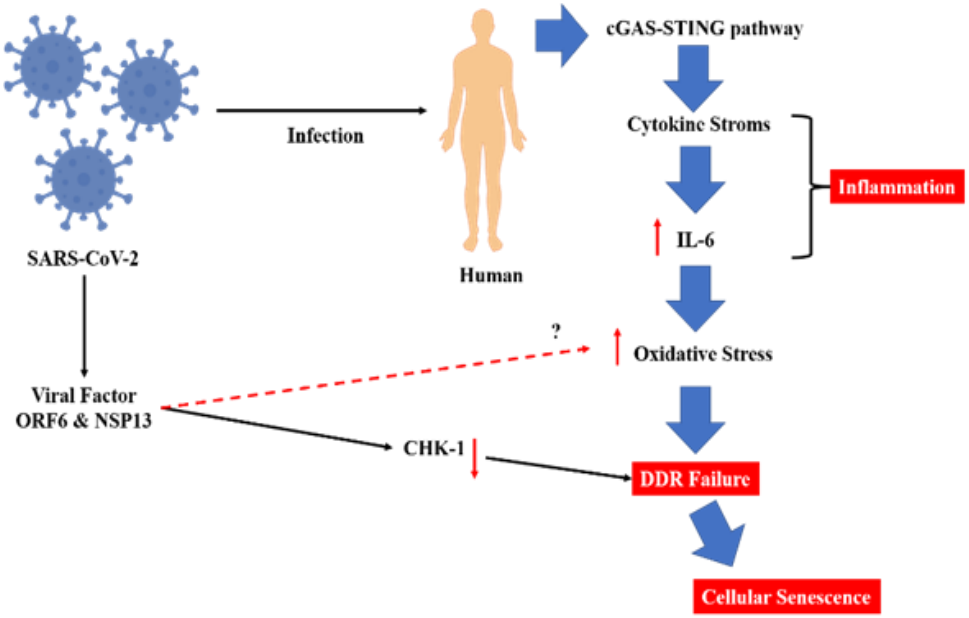

Figure 1. Prediction pathway of cellular senescence in SARS-CoV-2 infection. A direct pathway occurs through the interaction of ORF6 and NSP13 with CHK1 which triggers DDR failure. Meanwhile, an indirect pathway in the inflammatory response leads to a cytokine storm through IL-6 secretion, which causes increased oxidative stress and triggers cellular senescence.

An in vivo study and in COVID-19 patients showed that SARS-CoV-2 infection can trigger DNA damage by disruption of the DDR pathway[26]. DNA damage due to degradation of CHK1 is triggered by two factors from the virus such as origin replication factor 6 (ORF6) and non-structural protein 13 (NSP13) (**Figure 1**)[27]. CHK1 degradation is carried out through autophagy and UBS pathways. A decrease in CHK1 triggers disruption and cells lose ribonucleotide reductase M2 (RRM2), a complex formed from ribonucleotide reductase (RNR)[28]. This leads to a reduction in deoxynucleoside triphosphate (dNTP), S phase failure, severity of DNA damage, and cell senescence. The N protein of SARS-CoV-2 was also identified to block the formation of transformation related protein 53 binding protein 1 (53BP1) or factors in the DNA repair complex through inhibiting the activity of damage-induced long non-coding RNAs (dilncRNAs)[29]. dilncRNAs under normal conditions can interact with DDR factors such as transformation related protein 53 (p53) for DNA repair activation[30]. In summary, SARS-CoV- 2 infection can affect nuclear DNA, this can lead to long-term effects such as the emergence of cancer and senescence. Although long-term SARS-CoV-2 infection is currently not known to be associated with lung cancer, evidence of phenotypic data on accelerated senescence has been reported.

Association of cellular senescence and inflammatory response due to SARS-CoV-2 infection

COVID-19 initiated by SARS-CoV-2 infection may trigger impaired innate and adaptive immune cell responses to secrete excess increases in pro-inflammatory cytokines[31]. Pro-inflammatory cytokines such as IL-6, TNF, and IL-18 have been reported to be significantly increased during SARS-CoV-2

infection due to immune response failure[32]. IL-6 is involved in the process of systemic inflammation that triggers complications in the patient's health. SARS-CoV-2 can trigger the activation of IL-6 secretion through the inflammatory pathway regulated by NF-κB and the formation of the inflammasome complex[33]. IL-6 can be produced by SARS-CoV-2 host cells such as most epithelial cells in the lung. When epithelial cells are lysed, IL-6 will be secreted to activate monocyte and macrophage responses. However, excessive release of IL-6 is reported to trigger a cytokine storm that adversely affects the patient[34].

DDR in the cell cytoplasmic environment can be detected by the cyclic guanosine monophosphate-adenosine monophosphate-stimulator of interferon genes (cGAS-STING) pathway, which can trigger an inflammatory response[35]. The presence of cGAS-STING and inflammatory response in cells after SARS-CoV-2 infection is indicated by the high number of micronuclei in infected cells[36]. DDR has been identified to trigger the accumulation of proinflammatory factor transcription consist of IL-6, IL-8, chemokine (C-X-C motif) 9 (CXCL9), chemokine (C-X-C motif) 10 (CXCL10), and TNF-α. SARS-CoV-2 infection can trigger damage to DNA and altered DDR, resulting in an inflammatory response that leads to cellular senescence[37,38]. The cGAS-STING pathway is important for immune cell responses to detect the presence of microbial DNA such as viruses and bacteria when infecting host cells. When invaders such as bacteria and viruses infect cells, cyclic guanosine monophosphate-adenosine monophosphate (cGAS) is activated to detect DNA from antigens and trigger the production of cyclic guanosine monophosphate (cGAMP)[39]. The compound can activate the STING pathway for the production of cytokines such as type 1 interferon (IFN-1) in response[40]. Activation of the cGAS-STING pathway may be associated with cellular aging due to chronic inflammatory responses. However, a role of the cGAS-STING pathway in senescence is not well understood and further research is needed.

The production of pro-inflammatory cytokines such as IL-6 during SARS-CoV-2 infection can initiate an increase in oxidative stress in cells and then trigger an acceleration in the senescence process[41,42]. The presence of oxidative stress can cause damage to DNA, cell membranes and proteins. Cellular senescence is also triggered by the senescence-associated secretory phenotype (SASP) pathway, which produces many pro-inflammatory molecules and several proteolytic enzymes that can cause damage to tissues, organs, and contribute to cellular senescence[43]. In summary, SARS-CoV-2 infection activates cGAS-STING to detect DNA damage, and activation of the pathway can trigger an inflammatory response through the production of pro-inflammatory cytokines such as IL-6 during infection. These pro-inflammatory cytokines lead to the production of excess oxidative stress and trigger more DNA damage, which accelerates the cellular aging process. The senescence associated secretory protein (SASP) pathway is another factor that contributes to cellular senescence by producing pro-inflammatory cytokines and proteolytic enzymes (**Figure 1**).

Conclusions

SARS-CoV-2 can accelerate cellular senescence by producing viral proteins such as ORF6 and NSP13 to disrupt DDR regulation through CHK1 degradation, CHK1 degradation triggers DDR failure for DNA repair and enhances the inflammatory response. Inflammation triggered by SARS-CoV-2 infection leads to cytokine storm signalling, it can increase the production of excess oxidative stress that accelerates the cellular senescence process.

Acknowledgments

This study was supported by a research grant from the Computational Virology Research Unit, Division of Molecular Biology and Genetics, Generasi Biologi Indonesia Foundation, Indonesia. We thank EJA Team, Indonesia for editing the manuscript.

Conflicts of Interest

There are not potential conflicts of interest.

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