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The emerging role of cellular senescence in complications of COVID-19

Md Mohiuddin, Kazuo Kasahara

Department of Respiratory Medicine, Kanazawa University, Kanazawa 920-8641, Ishikawa, Japan

A R T I C L E   I N F O

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A B S T R A C T

The coronavirus disease 2019 (COVID-19) pandemic has triggered a sudden global change in healthcare systems. Cancer patients have a higher risk of death from COVID-19 in comparison to patients without cancer. Many studies have stated that various factors, such as older age, frequent exposure to healthcare, and higher smoking rates are responsible for the complications of COVID-19. We hypothesize that side effects of chemotherapy, such as cellular senescence, could worsen COVID-19. Given this situation, in this review, we highlight the updated findings of research investigating the impact of cellular senescence on COVID-19 complications and explored potential therapeutic targets for eliminating senescent cells during the COVID-19 pandemic.

Introduction

Early studies of COVID-19 infected cancer patients reported that they showed a higher mortality rate in comparison to the general public [1, 2]. Patients with thoracic cancer are considered to be at increased risk their age, smoking status, pre-existing comorbidities, and chemotherapy selection should be considered in the treatment of their disease [3,4]. Many chemotherapy drugs induce cellular senescence, which can trigger cancer metastasis and relapses and various adverse reactions to cancer treatments [5–7]. Thus, the COVID-19 pandemic has exposed and exacerbated the health system’s weaknesses around the world [8].

Cellular senescence is a physiological phenotype intended for the permanent arrest of the cell cycle and is morphologically identified as flattening, enlargement of the nucleus and nucleoli and the appearance of vacuoles in the cytoplasm [9,10]. We hypothesize that it will be necessary to clarify the possible association of cellular senescence with complications of COVID-19, which will challenge us to develop new therapeutic approaches to eliminate cellular senescence in cancer patients during the COVID-19 pandemic.

This review describes updated studies on the association between cellular senescence and COVID-19. This study also provides instructions for developing a promising treatment to clear senescent cells during the COVID-19 pandemic.

The link between COVID-19 and cellular senescence: clinical and preclinical evidence

SARS-CoV-2 is a novel coronavirus that infects the lower respiratory tract and which can cause coronavirus disease 2019 (COVID-19), a complex respiratory distress syndrome [11]. Cellular senescence, a stable stunting state characterized by pro-inflammatory and pro-disease mechanisms associated with senescence before and after SARS-CoV-2 infection could have the potential to limit the range of severe harm and improve the effectiveness of vaccines [15]. Another study proposed that micro-dose lithium treatment could protect cells from senescence and the development of conditions related to aging [16]. The previous study also suggested the potential use of low-dose lithium in elderly patients in the 'high-risk group' for COVID-19 [16]. Another study reported that aging plays a role in several infectious diseases, including SARS-CoV-2 infection [17]. A previous study provided a novel direction that showed a crucial and interdependent association with different cellular pathways, e.g., mitochondrial, telomere, and cellular senescence in association with SARS-CoV-2 COVID-19 proteins [17]. Biasi et al. [18] stated that patients show significant increases in pro-inflammatory or anti-inflammatory cytokines, including T helper type-1 and type-2 cytokines, chemokines and galectins; their lymphocytes produce more tumor necrosis factor (TNF), interferon-γ, interleukin (IL) –2 and IL-17, and the latest observation implies that blocking IL-17 could provide a new therapeutic strategy for COVID-19. Omarjee et al. [19] reported
that a decreased T-cell count, and functional depletion and cytokine release syndrome were identified as adverse factors in patients with severe SARS-CoV-2 infection. Therefore, severe COVID-19 can mimic a state of immune senescence [19]. A previous study claimed that palitaxel could be a promising cancer drug and could offer a new therapeutic strategy for gefitinib-resistant non-small cell lung cancer (NSCLC) during the COVID-19 pandemic [20]. The antiviral cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway has been newly proven to regulate senescence phenotypes [21]. Another study stated that prolonged exposure to IFN-γ and IL-6 were shown to induce senescence in normal cells, suggesting that infected—but not necessarily senescent—cells could trigger senescence in the surrounding environment [12]. A previous study reported that infected cells activate antiviral responses that include the release of type I and III interferons (IFNs) and other pro-inflammatory mediators [22]. Another study indicated that cellular senescence could be induced prematurely by viral infections through cellular or non-cellular autonomic mechanisms [23]. Some viruses can damage DNA or cell fusion and cause a state of cellular senescence [24–26]. SARS-CoV and SARS-CoV-2 trigger a "cytokine storm," releasing a series of inflammatory cytokines and chemokines, such as CXCL-10, CCL-2, IL-6 IL-8, IL-12, IL-1β, IFN-γ and TNF-α [27].

Many of these factors have the potential to induce "paracrine" senescence through prolonged cytokine signaling [27–29]. All preclinical and clinical studies have attempted to elucidate a possible connection between cellular senescence and COVID-19. However, more studies are needed to fully establish this association.

### Potential therapeutic targets for eliminating cellular senescence

Cellular senescence is considered a double-edged sword [30]. Senescent cells can promote chronic inflammation when senescent cells are retained [31], which can make COVID-19 worse [12]. Therefore, the targeted removal of senescent cells has emerged as a promising new opportunity for therapeutic interventions [32]. Currently, researchers have confirmed several molecular targets for the elimination of senescent cells (Fig. 1).

- **Mitogen-activated protein kinases (MAPKs)** can detect changes in cellular conditions and, in turn, elicit adaptive responses, including cellular senescence [33]. MAPKs modulate the levels and functions of many proteins, including pro-inflammatory factors and factors in the p21/p53 and p16/Rb pathways, the primary regulatory axes of senescence [33]. Through these actions, MAPKs implement the key features of senescence: growth arrest, cell survival, and the secretory senescence-associated phenotype (SASP) [33]. The use of MAPK inhibitors can help to eliminate cellular senescence [34].

- The activation of AMPK is helpful for cellular homeostasis and the prevention of senescence [35]. However, the molecular events involved in AMPK activation are not well defined [35]. Another study claimed that AMPK reduced the expression of genes involved in cellular senescence in human lung epithelial cells [36]. Senescent cells are non-dormant cells that exhibit an increased inflammatory phenotype in response to stress [37]. Therefore, AMPK activation can assist in eliminating cellular senescence [38].

- **ROS results as a tightly regulated signaling process for the induction of cellular senescence** [39]. High levels of ROS mediate p53 activation, which induces the inhibition of autophagy [39]. This event generates mitochondrial dysfunction, which in turn causes cellular senescence [39]. Therefore, maintaining the correct balance of ROS in cells is crucial for relieving senescence [40].

- mTOR goes far beyond proliferation and coordinates a metabolic program tailored to cells to control cell growth and many biological processes, including cell aging and senescence [41]. Interestingly, many senescence phenotypes are regulated by mTORC1 in various cell types [42]. The secretion of pro-inflammatory mediators by senescent cells contributes to aging and has been termed the senescence-associated secretory phenotype (SASP) [43]. Recent studies have identified an essential role for mTORC1 in the promotion of SASP [44,45]. Therefore, an mTOR inhibitor could eliminate cellular senescence [46].

- **SIRT1 (Sir2) is an NAD+-dependent deacetylase that plays a critical role in a wide range of biological events, including metabolism, the immune response, and aging** [47]. Autophagy, a catabolic pathway of membrane trafficking that degrades cellular components via autophagosomes and lysosomes, mediates the downregulation of mammalian SIRT1 protein during senescence [48]. Upon senescence, nuclear SIRT1 is recognized as a substrate for autophagy and undergoes autophagosome-lysosome cytoplasmic degradation via autophagic protein LC3 [48]. Therefore, SIRT1 activation can provide a new target to clear senescent cells [49].

- **The JAK pathway** is more activated in senescent cells than in non-senescent cells [50]. The inhibition of the JAK pathway suppresses SASP in senescent cells and alleviates age-related tissue dysfunction [50]. A previous study reported that the JAK pathway is activated in adipose tissue with aging, and SASP can be suppressed by inhibiting the JAK pathway in senescent cells [51]. Therefore, the inhibition of the JAK pathway could remove cellular senescence [52].

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**Senescent cells**

**Therapeutic targets**

- MAPK
- NF-κB
- AMPK
- ROS
- mTOR
- SIRT1
- JAK
- ROCK
- IKK/NF-κB
- Prelamine A
- p53/p21
- p16/Rb

**Fig. 1.** Various therapeutic targets to remove cellular senescence. The elimination of cellular senescence generated by senescent cells is considered therapeutically beneficial. However, if senescent cell elimination does not occur, this can worsen COVID-19 in cancer patients. MAPK, Mitogen-activated protein kinase; NF-κB, Nuclear factor kappa light chain enhancer of activated B cells; AMPK, AMP-activated protein kinase; ROS, Reactive oxygen species; mTOR, Mammalian target of rapamycin; SIRT1, Sirtuin-1; JAK, Janus kinase; ROCK, Rho-associated protein kinase; IKK, IκB kinase; Rb, Retinoblastoma protein.
Author contributions
M.M. prepared the draft; M.M. and K.K. conceptualized and edited the article. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest
The authors declare no competing financial interests.

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