Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Cellular senescence is a potential severity factor for COVID-19: Suitable targets required to eliminate cellular senescence

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that has resulted in a global pandemic. As of May 13, 2021, this emerging infection was reported to have caused 160,074,267 infections and 3,325,260 deaths [1]. Cancer patients have an increased risk of death from COVID-19 compared to non-cancer patients [2]. Preliminary studies have reported that cellular senescence can worsen the COVID-19 pandemic [3–5]. A recent study stated that targeting mechanisms associated with senescence before and after SARS-CoV-2 infection have the potential to limit the range of severe harm and improve vaccine efficacy [6]. Another study reported that aging plays a vital role in numerous infectious diseases, including SARS-CoV-2 infection [7]. Therefore, it is crucial to clarify the factors that enhance cellular senescence in cancer patients and to investigate the appropriate treatment in order to minimize the severity of the COVID-19 pandemic.

COVID-19 triggers the release of several inflammatory chemokines and cytokines, including TNFα, IL-6, CXCL-10, IL-8, IFN-γ, IL-12, CCL-2 and IL-1β [8]. Many of these cytokines can exacerbate senescence through the prolongation of cytokine signaling [8]. Several studies have reported that older COVID-19 patients may have a high degree of cellular senescence [3,9]. Therefore, targeting cytokine storms with suitable drugs (e.g. rapamycin) can prevent the severe progression of COVID-19 [10,11].

Cytotoxic drugs are commonly used as cancer therapies, and many agents inhibit proliferation via cell cycle mechanisms [12]. Cellular senescence is a process in which cells irreversibly lose the ability to proliferate [13]. Several studies have claimed that the p53/p21 and p16/Rb signaling pathways regulate cellular senescence [14,15]. Therefore, inhibiting the p53/p21 and p16/Rb pathways may be a promising target for minimizing cellular senescence.

An increase in reactive oxygen species (ROS) production is related to cellular senescence [16]. A high ROS level can induce the activation of p53, which can then induce the inhibition of autophagy [17]. This effect triggers mitochondrial dysfunction, consequently inducing cellular senescence [17]. Therefore, maintaining the balance in the ROS levels will be useful for mitigating cellular senescence.

Mitogen-activated protein kinase (MAPK) has been reported to play a crucial role in senescent cells through the activation of Ras-Raf and the shortening of telomeres [18]. MAPKs modulate the levels and function of many proteins, including pro-inflammatory factors and factors in the p21/p53 and p16/Rb pathways, the principal regulatory axes of senescence [14]. TAK1, a mitogen-activated protein kinase (MAP3K), represses the transcription of the human telomerase reverse transcriptase (hTERT) gene in human cancer cells and induces cellular senescence in normal human diploid cells [19]. Oncogenic Ras transforms immortal rodent cells into a tumorigenic state, partly through the constitutive transmission of mitogenic signals through the MAPK cascade [20]. Ras is initially mitogenic in primary cells but eventually induces premature senescence, involving the tumor suppressors p53 and p16INK4a [20]. Therefore, MAPK inhibitors can help eliminate cellular senescence.

Mammalian targets of rapamycin (mTOR) kinase, an essential component of mTOR complex 1 (mTORC1) and mTORC2, binds directly to p53 and phosphorylates it to serine 15 [21]. mTORC1 and mTORC2 compete with MDM2 and increase the stability of p53 to induce cellular senescence through the accumulation of the cell cycle inhibitor p21 [21]. A previous study reported that mTORC1 and cellular senescence are closely linked to both each other and the host organism's aging [22]. Therefore, mTOR inhibition may be a suitable target for eliminating senescent cells.

In conclusion, due to the COVID-19 pandemic, clinical data on the association between cellular senescence and COVID-19 severity are lacking. There will likely be greater efforts to study the impact of cellular senescence on COVID-19 complications in the future. Therefore, exploring potential targets for minimizing cellular senescence and assessing them in clinical trials may save many lives during the COVID-19 pandemic.

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