

Impact of Cellular Senescence on Neurodegenerative Diseases during the COVID-19 Pandemic: Suitable Targets Required to Eliminate Cellular Senescence

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We recently reviewed the scientific literature that elucidates the impact of cellular senescence on COVID-19 complications [1]. Recent studies have discussed the association of cellular senescence in COVID-19 patients with neurodegenerative diseases [2-5]. Therefore, in the present study, we extend this scientific synopsis to comment on how cellular senescence can promote neurodegenerative diseases and to describe suitable targets for eliminating cellular senescence.

Cellular senescence is a phenomenon characterized by a stable and terminal stage of growth arrest [6]. During cellular senescence, phenotypic changes can occur, known as senescence-associated secretory phenotype (SASP) [7]. Persistent senescent cells cause age-related diseases, while the induction of acute senescence protects against cancer [6]. Thus, targeting senescent cells to limit cellular aging by administering appropriate drugs—called senolytics—could effectively remove senescent cells [8].

The induction of cellular senescence is regulated by excessive ROS production [9]. In contrast, high ROS levels can mediate the activation of p53, which triggers the activation of autophagy [10]. This cellular process triggers mitochondrial dysfunction, which is related to the induction of cellular senescence [11]. ROS have been reported to alter various cellular functions through DNA damage, promoting certain human diseases, such as cancer and neurodegenerative disease [12]. Thus, the implementation of ROS production inhibitors to maintain a correct ROS balance could reduce cellular senescence.

Peripheral immune cells, astrocytes, microglia, and neurons can secrete cytokine molecules into the central nervous system (CNS) [13]. The upregulation of cytokines

and their receptors in the brain is characterized as peripheral or central inflammation [14]. Inflammation has been reported to play an important role in the central nervous system for various neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease [15,16]. Notably, interleukin (IL)-6, a pro-inflammatory cytokine, is elevated in patients with Alzheimer's disease [17]. In addition, β -amyloid (A β) peptide deposition promotes a spectrum of activated microglia-mediated brain neuroinflammation, causing the expression of various inflammatory cytokines, including IL-6, tumor necrosis factor- α (TNF- α) and IL-1 β [17]. Conversely, pro-inflammatory cytokines, such as IL-6 and IL-8 are also present in SASP [18]; therefore, cytokine inhibitors could be useful in targeting and eliminating cellular senescence.

NF- κ B is a transcription factor involved in the control of a large number of cellular processes, including cell survival, immune and inflammatory responses, and apoptosis [19]. NF- κ B has been reported to be activated by cell damage and stress, resulting in increased activity with chronic aging-related diseases [20]. Furthermore, NF- κ B signaling is the main inducer of cellular senescence [21]. Aging is the most significant risk factor for the development of Alzheimer's disease, and recent findings have shown tissue-specific brain inflammation mediated by NF- κ B in Alzheimer's disease [22,23]. Therefore, inhibition of the NF- κ B pathway could be a suitable approach to eliminating cellular senescence and targeting the onset of AD.

mTOR is a member of the phosphatidylinositol 3-kinase family of protein kinases [24]. mTOR binds to other proteins and serves as a central component of two distinct protein complexes, mTOR complex 1 and mTOR complex 2, which regulate different cellular processes [25]. Mammalian

target of rapamycin complex 1 (mTORC1) and cellular senescence have been reported to be closely related to each other and to organism aging [26]. Furthermore, mTOR regulates cellular senescence by modulating mitochondrial metabolism, autophagy, and protein translation [27]. A previous study claimed that mTOR plays a role in several neurodegenerative diseases, including Down syndrome, Alzheimer's disease, and Huntington's disease [28]. Therefore, mTOR inhibition could be a suitable strategy for eliminating cellular senescence.

In conclusion, emerging evidence has demonstrated that cellular senescence is related to neurodegenerative diseases. Furthermore, preliminary studies have indicated that cellular senescence could exacerbate the complications of COVID-19. Due to the COVID-19 pandemic, limited preclinical and clinical studies have investigated the impact of cellular senescence on complications of COVID-19 in patients with neurodegenerative disorders. However, we anticipate that there will soon be greater efforts to fully establish the role of cellular senescence in COVID-19 patients with neurodegenerative disease.

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing Interests

The authors declare no conflicts of interest in association with the present study.

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