
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.

Cancer Treatment and Research Communications 28 (2021) 100399

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Review Article

# 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*

ARTICLE INFO

*Keywords:*
Senescence
COVID-19
Pandemic
Chemotherapy
Cancer

ABSTRACT

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 functions, may hypothetically contribute to the pathogenesis of COVID-19 and a potential pharmaceutical target for alleviating disease severity [12]. Many studies have revealed that cellular senescence may be related to the worsening of COVID-19 [12–14]; however, this link is still unclear.

The measurement of cellular senescence bursts could hypothetically serve as a predictor of the severity of COVID-19. The targeting 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 microdose 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

* Corresponding author.
*E-mail address:* mohiuddin@med.kanazawa-u.ac.jp (M. Mohiuddin).

https://doi.org/10.1016/j.ctarc.2021.100399

Available online 15 May 2021

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 paclitaxel 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).

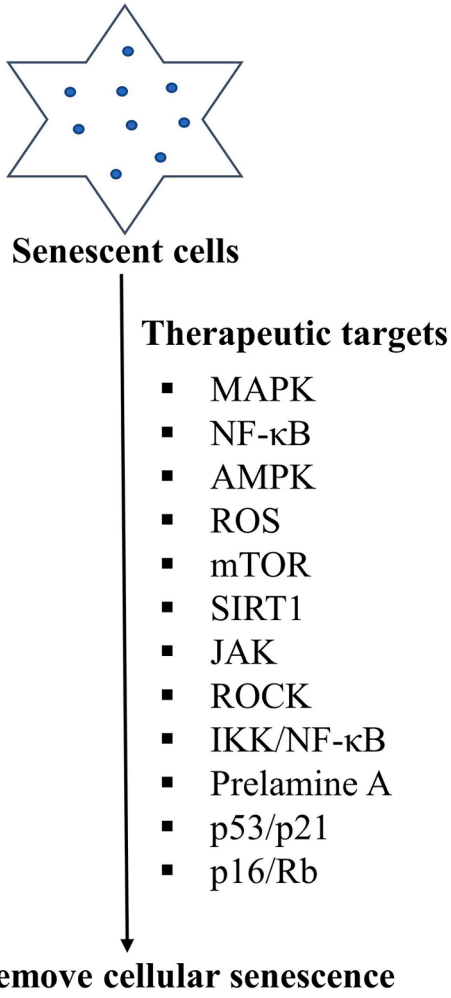


**Fig. 1.** Various therapeutic targets to remove cellular senescence. The elimination of cellular senescence generated by senescent cells is considered therapeutically beneficial. However, if senescent cell elimination does not occur, this can worsen COVID-19 in cancer patients. MAPK, Mitogen-activated 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.

- 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].

- Rho-associated kinases 1 and 2 (ROCK1/2) are Rho-GTPase effectors that control key aspects of the actin cytoskeleton; however, their role in proliferation and cancer initiation or progression is unknown [53]. Additionally, ROCK1 and ROCK2 act redundantly to maintain actomyosin contractility and cell proliferation, and their loss leads to cell cycle arrest and cell senescence [53]. This phenotype results from the downregulation of the essential cell cycle proteins Cyclin A, CKS1 and CDK1 [53]. Therefore, ROCK inhibition could open up a new spectrum for the removal of cellular senescence [32,54,55].
- The NF-κB system is an evolutionarily conserved signaling pathway triggered by immune activation and various external and internal warning signs associated with senescence and the aging process, such as oxidative and genotoxic stress [56]. Activation of the NF-κB system is linked to several pattern recognition receptor pathways, for example, TLRs and inflammasomes, and the signaling of many upstream kinase cascades via canonical and IKKα/β and NIK non-canonical pathways are the most critical upstream kinases [57,58]. However, various kinases can directly regulate the transcriptional capacity of NF-κB factors [59]. While many studies have shown the antitumor and pro-survival role of NF-κB in cancer cells, recent findings raise the possibility that NF-κB participates in a senescence-associated cytokine response, suggesting a tumor-limiting role of NF-κB [60,61]. Therefore, inhibition of the IKK/NF-κB pathway could be a promising target to reduce cellular senescence [34,62].
- The accumulation of progerin and prelamine A are hallmarks of a group of premature aging diseases [63]. They have also been found during normal cellular aging, strongly suggesting similar mechanisms between healthy aging and LMNA-related progeroid syndromes [63]. It is not clear how this toxic buildup contributes to aging (physiological or pathological) [63]. A previous study reported that the accumulation of progerin in HGPS cells leads to aberrant nuclear morphology, genetic instability, and p53-dependent premature senescence [64]. Progerin and prelamine A inhibition may provide potential therapeutic approaches to the removal of cellular senescence [65,66].
- Numerous studies have shown that p53/p21 pathway is involved in regulating cellular senescence [67-69]. p16-mediated senescence acts through the retinoblastoma (Rb) pathway, inhibiting the action of cyclin-dependent kinases that lead to the arrest of the G1 cell cycle [70]. Rb is maintained in a hypophosphorylated state, resulting in the inhibition of the transcription factor E2F1 [71,72]. Therefore, inhibition of the p53/p21 and p16/Rb pathways represents a promising target for the elimination of cellular senescence [73,74].

## Conclusion

Senescent cells cause several age-related diseases, accounting for a high percentage of all causes of death worldwide and expanding morbidity. Cellular senescence could worsen the COVID-19 pandemic; however, due to the pandemic, the data available to support this association are limited and further study is required. We expect that there will be increased efforts to explore the impact of cellular senescence on COVID-19. In the future, clinical trials focused on eliminating senescent cells to determine specific treatments and markers to evaluate therapeutic efficacy will be imperative. This brief review attempted to describe updated studies focused on the elucidation of the impact of cellular senescence in the COVID-19 pandemic. The present study highlighted some of the molecular biomarkers and pathways responsible for cellular senescence, which can be explored as potential targets for overcoming cellular senescence.

## 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.

## Funding statement

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors. The APC was funded by Kanazawa University, Department of Respiratory Medicine, Kanazawa 920–8641, Ishikawa, Japan.

## Declaration of Competing Interest

The authors declare no competing financial interests.

## References

[1] K.S. Saini, M. Tagliamento, M. Lambertini, R. McNally, M. Romano, M. Leone, G. Curigliano, E. de Azambuja, Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies, Eur. J. Cancer 139 (2020) 43–50, https://doi.org/10.1016/j.ejca.2020.08.011.
[2] B.L. Ferrari, C.G. Ferreira, M. Menezes, P. De Marchi, J. Canedo, A.C. Melo, A. A. Jacome, T. Reinert, R.D. Paes, B. Sodre, et al., Determinants of COVID-19 mortality in patients with cancer from a community oncology practice in Brazil, JCO Glob. Oncol. 7 (2021) 46–55, https://doi.org/10.1200/GO.20.00444.
[3] C. Leduc, D. Antoni, A. Charloux, P.E. Falcoz, E. Quoix, Comorbidities in the management of patients with lung cancer, Eur. Respir. J. (2017) 49, https://doi.org/10.1183/13993003.01721-2016.
[4] A.S. Pathania, P. Prathipati, B.A. Abdul, S. Chava, S.S. Katta, S.C. Gupta, P. R. Gangula, M.K. Pandey, D.L. Durden, S.N. Byrareddy, et al., COVID-19 and Cancer comorbidity: therapeutic opportunities and challenges, Theranostics 11 (2021) 731–753, https://doi.org/10.7150/thno.51471.
[5] J.A. Ewald, J.A. Desotelle, G. Wilding, D.F. Jarrard, Therapy-induced senescence in cancer, J. Natl. Cancer Inst. 102 (2010) 1536–1546, https://doi.org/10.1093/jnci/djq364.
[6] M. Demaria, M.N. O'Leary, J. Chang, L. Shao, S. Liu, F. Alimirah, K. Koenig, C. Le, N. Mitin, A.M. Deal, et al., Cellular senescence promotes adverse effects of chemotherapy and cancer relapse, Cancer Discov. 7 (2017) 165–176, https://doi.org/10.1158/2159-8290.CD-16-0241.
[7] Mohiuddin, M.; Kimura, H.; Sone, T.; Matsuoka, H.; Saeki, K.; Terada, N.; Nguyen, M.A.T.; Kasahara, K. Pemetrexed disodium heptahydrate suppressed apoptosis by pRb hyperphosphorylation and CDKs overexpression in PC9 cells. In Proceedings of CANCER SCIENCE; pp. 327-327.
[8] A. Lal, N.A. Erondu, D.L. Heymann, G. Gitahi, R. Yates, Fragmented health systems in COVID-19: rectifying the misalignment between global health security and universal health coverage, Lancet 397 (2021) 61–67.
[9] K. Tominaga, The emerging role of senescent cells in tissue homeostasis and pathophysiology, Pathobiol. Aging Age Relat. Dis. 5 (2015) 27743, https://doi.org/10.3402/pba.v5.27743.
[10] D.G. Burton, R.G. Faragher, Cellular senescence: from growth arrest to immunogenic conversion, Age (Dordr) 37 (2015) 27, https://doi.org/10.1007/s11357-015-9764-2.
[11] I. Astuti, Ysrafil, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response, Diabetes Metab. Syndr. 14 (2020) 407–412, https://doi.org/10.1016/j.dsx.2020.04.020.
[12] J. Nehme, M. Borghesan, S. Mackedenski, T.G. Bird, M. Demaria, Cellular senescence as a potential mediator of COVID-19 severity in the elderly, Aging Cell 19 (2020) e13237, https://doi.org/10.1111/acel.13237.
[13] Y. Chen, S.L. Klein, B.T. Garibaldi, H. Li, C. Wu, N.M. Osevala, T. Li, J.B. Margolick, G. Pawelec, S.X. Leng, Aging in COVID-19: vulnerability, immunity and intervention, Ageing Res. Rev. 65 (2021), 101205, https://doi.org/10.1016/j.arr.2020.101205.
[14] L.S. Cox, I. Bellantuono, J.M. Lord, E. Sapey, J.B. Mannick, L. Partridge, A. L. Gordon, C.J. Steves, M.D. Witham, Tackling immunosenescence to improve COVID-19 outcomes and vaccine response in older adults, Lancet Healthy Longev. 1 (2020) e55–e57, https://doi.org/10.1016/S2666-7568(20)30011-8.
[15] J. Nehme, M. Borghesan, S. Mackedenski, T.G. Bird, M. Demaria, Cellular senescence as a potential mediator of COVID-19 severity in the elderly, Aging Cell 19 (2020) e13237.
[16] T. Viel, S. Chinta, A. Rane, M. Chamoli, H. Buck, J. Andersen, Microdose lithium reduces cellular senescence in human astrocytes - a potential pharmacotherapy for COVID-19? Aging (Albany NY) 12 (2020) 10035–10040, https://doi.org/10.18632/aging.103449.
[17] K.P. Maremanda, I.K. Sundar, D. Li, I. Rahman, Age-dependent assessment of genes involved in cellular senescence, telomere, and mitochondrial pathways in human lung tissue of smokers, COPD, and IPF: associations With SARS-CoV-2 COVID-19 ACE2-TMPRSS2-Furin-DPP4 Axis, Front. Pharmacol. 11 (2020) 1356.
[18] S. De Biasi, M. Meschiari, L. Gibellini, C. Bellinazzi, R. Borella, L. Fidanza, L. Gozzi, A. Iannone, D. Lo Tartaro, M. Mattioli, et al., Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia, Nat. Commun. 11 (2020) 3434, https://doi.org/10.1038/s41467-020-17292-4.
[19] L. Omarjee, A. Janin, F. Perrot, B. Laviolle, O. Meilhac, G. Mahe, Targeting T-cell senescence and cytokine storm with rapamycin to prevent severe progression in

COVID-19, Clin. Immunol. 216 (2020), 108464, https://doi.org/10.1016/j.clim.2020.108464.
[20] M. Mohiuddin, K. Kasahara, Abstract P27: Effect of Paclitaxel in Gefitinib-Resistant Non-Small Cell Lung Cancer (NSCLC) Treatment During the COVID-19 Pandemic, AACR, 2021.
[21] T. Li, Z.J. Chen, The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer, J. Exp. Med. 215 (2018) 1287–1299, https://doi.org/10.1084/jem.20180139.
[22] L.B. Ivashkiv, L.T. Donlin, Regulation of type I interferon responses, Nat. Rev. Immunol. 14 (2014) 36–49, https://doi.org/10.1038/nri3581.
[23] S. He, N.E. Sharpless, Senescence in health and disease, Cell 169 (2017) 1000–1011, https://doi.org/10.1016/j.cell.2017.05.015.
[24] A. Chuprin, H. Gal, T. Biron-Shental, A. Biran, A. Amiel, S. Rozenblatt, V. Krizhanovsky, Cell fusion induced by ERVWE1 or measles virus causes cellular senescence, Genes Dev. 27 (2013) 2356–2366, https://doi.org/10.1101/gad.227512.113.
[25] R. Seoane, S. Vidal, Y.H. Bouzaher, A. El Motiam, C. Rivas, The interaction of viruses with the cellular senescence response, Biology (Basel) 9 (2020), https://doi.org/10.3390/biology9120455.
[26] W.J. Kelley, R.L. Zemans, D.R. Goldstein, Cellular senescence: friend or foe to respiratory viral infections? Eur. Respir. J. 56 (2020) https://doi.org/10.1183/13993003.02708-2020.
[27] F. Coperchini, L. Chiovato, L. Croce, F. Magri, M. Rotondi, The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system, Cytokine Growth Factor Rev. 53 (2020) 25–32, https://doi.org/10.1016/j.cytogfr.2020.05.003.
[28] Y. Tang, J. Liu, D. Zhang, Z. Xu, J. Ji, C. Wen, Cytokine storm in COVID-19: the current evidence and treatment strategies, Front. Immunol. 11 (2020) 1708, https://doi.org/10.3389/fimmu.2020.01708.
[29] M. Merad, J.C. Martin, Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages, Nat. Rev. Immunol. 20 (2020) 355–362, https://doi.org/10.1038/s41577-020-0331-4.
[30] N. Ohtani, A. Takahashi, D.J. Mann, E. Hara, Cellular senescence: a double-edged sword in the fight against cancer, Exp. Dermatol. 21 (Suppl 1) (2012) 1–4, https://doi.org/10.1111/j.1600-0625.2012.01493.x.
[31] L. Prata, I.G. Ovsyannikova, T. Tchkonia, J.L. Kirkland, Senescent cell clearance by the immune system: emerging therapeutic opportunities, Semin. Immunol. 40 (2018), 101275, https://doi.org/10.1016/j.smim.2019.04.003.
[32] C. von Kobbe, Targeting senescent cells: approaches, opportunities, challenges, Aging (Albany NY) 11 (2019) 12844–12861, https://doi.org/10.18632/aging.102557.
[33] C. Anerillas, K. Abdelmohsen, M. Gorospe, Regulation of senescence traits by MAPKs, Geroscience 42 (2020) 397–408, https://doi.org/10.1007/s11357-020-00183-3.
[34] Y. Ovadya, V. Krizhanovsky, Strategies targeting cellular senescence, J. Clin. Invest. 128 (2018) 1247–1254, https://doi.org/10.1172/JCI95149.
[35] X. Han, H. Tai, X. Wang, Z. Wang, J. Zhou, X. Wei, Y. Ding, H. Gong, C. Mo, J. Zhang, et al., AMPK activation protects cells from oxidative stress-induced senescence via autophagic flux restoration and intracellular NAD(+) elevation, Aging Cell 15 (2016) 416–427, https://doi.org/10.1111/acel.12446.
[36] X.Y. Cheng, Y.Y. Li, C. Huang, J. Li, H.W. Yao, AMP-activated protein kinase reduces inflammatory responses and cellular senescence in pulmonary emphysema, Oncotarget 8 (2017) 22513–22523, https://doi.org/10.18632/oncotarget.15116.
[37] B.G. Childs, M. Gluscevic, D.J. Baker, R.M. Laberge, D. Marquess, J. Dananberg, J. M. van Deursen, Senescent cells: an emerging target for diseases of ageing, Nat. Rev. Drug Discov. 16 (2017) 718–735, https://doi.org/10.1038/nrd.2017.116.
[38] A.L. Stancu, AMPK activation can delay aging, Discoveries (Craiova) 3 (2015) e53, https://doi.org/10.15190/d.2015.45.
[39] P. Davalli, T. Mitic, A. Caporali, A. Lauriola, D.ROS D'Arca, Cell senescence, and novel molecular mechanisms in aging and age-related diseases, Oxid. Med. Cell Longev. 2016 (2016), 3565127, https://doi.org/10.1155/2016/3565127.
[40] B.L. Tan, M.E. Norhaizan, W.P. Liew, H. Sulaiman Rahman, Antioxidant and oxidative stress: a mutual interplay in age-related diseases, Front. Pharmacol. 9 (2018) 1162, https://doi.org/10.3389/fphar.2018.01162.
[41] T. Weichhart, mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review, Gerontology 64 (2018) 127–134, https://doi.org/10.1159/000484629.
[42] S. Xu, Y. Cai, Y. Wei, mTOR signaling from cellular senescence to organismal aging, Aging Dis. 5 (2014) 263–273, https://doi.org/10.14336/AD.2014.0500263.
[43] J.M. van Deursen, The role of senescent cells in ageing, Nature 509 (2014) 439–446, https://doi.org/10.1038/nature13193.
[44] R.M. Laberge, Y. Sun, A.V. Orjalo, C.K. Patil, A. Freund, L. Zhou, S.C. Curran, A. R. Davalos, K.A. Wilson-Edell, S. Liu, et al., MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation, Nat. Cell Biol. 17 (2015) 1049–1061, https://doi.org/10.1038/ncb3195.
[45] S. Watanabe, S. Kawamoto, N. Ohtani, E. Hara, Impact of senescence-associated secretory phenotype and its potential as a therapeutic target for senescence-associated diseases, Cancer Sci. 108 (2017) 563–569, https://doi.org/10.1111/cas.13184.
[46] R. Iglesias-Bartolome, V. Patel, A. Cotrim, K. Leelahavanichkul, A.A. Molinolo, J. B. Mitchell, J.S. Gutkind, mTOR inhibition prevents epithelial stem cell senescence and protects from radiation-induced mucositis, Cell Stem Cell 11 (2012) 401–414, https://doi.org/10.1016/j.stem.2012.06.007.
[47] S. Imai, L. Guarente, Ten years of NAD-dependent SIR2 family deacetylases: implications for metabolic diseases, Trends Pharmacol. Sci. 31 (2010) 212–220, https://doi.org/10.1016/j.tips.2010.02.003.
[48] C.Y. Xu, L. Wang, P. Fozouni, G. Evjen, V. Chandra, J. Jiang, C.C. Lu, M. Nicastri, C. Bretz, J.D. Winkler, et al., SIRT1 is downregulated by autophagy in senescence and ageing, Nat. Cell Biol. 22 (2020), 1170-+.
[49] W. Grabowska, E. Sikora, A. Bielak-Zmijewska, Sirtuins, a promising target in slowing down the ageing process, Biogerontology 18 (2017) 447–476, https://doi.org/10.1007/s10522-017-9685-9.
[50] M. Xu, T. Tchkonia, J.L. Kirkland, Perspective: targeting the JAK/STAT pathway to fight age-related dysfunction, Pharmacol. Res. 111 (2016) 152–154, https://doi.org/10.1016/j.phrs.2016.05.015.
[51] M. Xu, T. Tchkonia, H.S. Ding, M. Ogrodnik, E.R. Lubbers, T. Pirtskhalava, T. A. White, K.O. Johnson, M.B. Stout, V. Mezera, et al., JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age, Proc. Natl Acad. Sci. USA 112 (2015) E6301–E6310.
[52] M. Xu, T. Tchkonia, H. Ding, M. Ogrodnik, E.R. Lubbers, T. Pirtskhalava, T. A. White, K.O. Johnson, M.B. Stout, V. Mezera, et al., JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) E6301–E6310, https://doi.org/10.1073/pnas.1515386112.
[53] S. Kumper, F.K. Mardakheh, A. McCarthy, M. Yeo, G.W. Stamp, A. Paul, J. Worboys, A. Sadok, C. Jorgensen, S. Guichard, et al., Rho-Associated Kinase (ROCK) Function is Essential for Cell Cycle progression, Senescence and Tumorigenesis, Elife, 2016, p. 5.
[54] M. Paez-Ribes, E. Gonzalez-Gualda, G.J. Doherty, D. Munoz-Espin, Targeting senescent cells in translational medicine, EMBO Mol. Med. 11 (2019) e10234, https://doi.org/10.15252/emmm.201810234.
[55] S. Niklander, D. Bandaru, D.W. Lambert, K.D. Hunter, ROCK inhibition modulates the senescence-associated secretory phenotype (SASP) in oral keratinocytes, FEBS Open Bio. 10 (2020) 2740–2749, https://doi.org/10.1002/2211-5463.13012.
[56] C.R. Balistreri, G. Candore, G. Accardi, G. Colonna-Romano, D. Lio, NF-kappaB pathway activators as potential ageing biomarkers: targets for new therapeutic strategies, Immun. Ageing (10) (2013) 24, https://doi.org/10.1186/1742-4933-10-24.
[57] T. Liu, L. Zhang, D. Joo, S.C. Sun, NF-kappaB signaling in inflammation, Signal Transduct. Target Ther. 2 (2017), https://doi.org/10.1038/sigtrans.2017.23.
[58] H. Yu, L. Lin, Z. Zhang, H. Zhang, H. Hu, Targeting NF-kappaB pathway for the therapy of diseases: mechanism and clinical study, Signal Transduct. Target Ther. 5 (2020) 209, https://doi.org/10.1038/s41392-020-00312-6.
[59] A. Oeckinghaus, S. Ghosh, The NF-kappaB family of transcription factors and its regulation, Cold Spring Harb. Perspect. Biol. 1 (2009), a000034, https://doi.org/10.1101/cshperspect.a000034.
[60] H. Jing, S. Lee, NF-kappaB in cellular senescence and cancer treatment, Mol. Cells 37 (2014) 189–195, https://doi.org/10.14348/molcells.2014.2353.
[61] M. Mussbacher, M. Salzmann, C. Brostjan, B. Hoesel, C. Schoergenhofer, H. Datler, P. Hohensinner, J. Basilio, P. Petzelbauer, A. Assinger, et al., Cell type-specific roles of NF-kappaB linking inflammation and thrombosis, Front. Immunol. 10 (2019) 85, https://doi.org/10.3389/fimmu.2019.00085.
[62] S. Vaughan, P.S. Jat, Deciphering the role of nuclear factor-kappaB in cellular senescence, Aging (Albany NY) 3 (2011) 913–919, https://doi.org/10.18632/aging.100390.
[63] A. Infante, A. Gago, G.R. de Eguino, T. Calvo-Fernandez, V. Gomez-Vallejo, J. Llop, K. Schlangen, A. Fullaondo, A.M. Aransay, A. Martin, et al., Prelamin A accumulation and stress conditions induce impaired Oct-1 activity and autophagy in prematurely aged human mesenchymal stem cell, Aging (Albany NY) 6 (2014) 264–280, https://doi.org/10.18632/aging.100651.
[64] K. Wheaton, D. Campuzano, W. Ma, M. Sheinis, B. Ho, G.W. Brown, S. Benchimol, Progerin-induced replication stress facilitates premature senescence in hutchinson-gilford progeria syndrome, Mol. Cell. Biol. (2017) 37, https://doi.org/10.1128/MCB.00659-16.
[65] A. Zhavoronkov, Z. Smit-McBride, K.J. Guinan, M. Litovchenko, A. Moskalev, Potential therapeutic approaches for modulating expression and accumulation of defective lamin A in laminopathies and age-related diseases, J. Mol. Med. (Berl) 90 (2012) 1361–1389, https://doi.org/10.1007/s00109-012-0962-4.
[66] S. Saxena, S. Kumar, Pharmacotherapy to gene editing: potential therapeutic approaches for Hutchinson-Gilford progeria syndrome, Geroscience 42 (2020) 467–494, https://doi.org/10.1007/s11357-020-00167-3.
[67] M. Mijit, V. Caracciolo, A. Melillo, F. Amicarelli, A. Giordano, Role of p53 in the regulation of cellular senescence, Biomolecules (2020) 10, https://doi.org/10.3390/biom10030420.
[68] Y. Qian, X. Chen, Senescence regulation by the p53 protein family, Methods Mol. Biol. 965 (2013) 37–61, https://doi.org/10.1007/978-1-62703-239-1_3.
[69] Z. Gu, J. Jiang, W. Tan, Y. Xia, H. Cao, Y. Meng, Z. Da, H. Liu, C. Cheng, p53/p21 Pathway involved in mediating cellular senescence of bone marrow-derived mesenchymal stem cells from systemic lupus erythematosus patients, Clin. Dev. Immunol. 2013 (2013), 134243, https://doi.org/10.1155/2013/134243.
[70] H. Rayess, M.B. Wang, E.S. Srivatsan, Cellular senescence and tumor suppressor gene p16, Int. J. Cancer 130 (2012) 1715–1725, https://doi.org/10.1002/ijc.27316.
[71] F.A. Dick, S.M. Rubin, Molecular mechanisms underlying RB protein function, Nat. Rev. Mol. Cell Biol. 14 (2013) 297–306, https://doi.org/10.1038/nrm3567.
[72] Mohiuddin, M.; Kimura, H.; Sone, T.; Matsuoka, H.; Nguyen, T.; Kasahara, K. Suppression of apoptosis by retinoblastoma protein hyperphosphorylation and cyclin-dependent kinases (CDKS) overexpression in lung adenocarcinoma cells,

induced by pemetrexed disodium heptahydrate. In Proceedings of Pediatr Blood Cancer; pp. S395-S395.

[73] A. Rufini, P. Tucci, I. Celardo, G. Melino, Senescence and aging: the critical roles of p53, Oncogene 32 (2013) 5129–5143.

[74] M. Mijit, V. Caracciolo, A. Melillo, F. Amicarelli, A. Giordano, Role of p53 in the regulation of cellular senescence, Biomolecules 10 (2020) 420.