Cell Senescence

Subjects: Cell Biology

Contributor: Sergey Lunin, Elena Novoselova, O. V. Glushkova

The ageing of an organism is based on the mechanisms that mediate the ageing of its cells, that is, cell senescence. Senescence is a programmed mechanism that protects cells, predominantly against DNA damage.

Keywords: cell senescence ; cell cycle ; immune response ; neuroendocrine regulators

1. Introduction

The ageing of an organism is based on the mechanisms that mediate the ageing of its cells, that is, cell senescence. Senescence is a programmed mechanism that protects cells, predominantly against DNA damage. Senescent cells stop dividing in response to mitogenic stimuli, and this condition is irreversible. In addition, such cells acquire certain morphological and functional changes that distinguish them from both the dividing and the resting (G0 phase) cells. Senescent cells partly retain their tissue-specific functions and therefore are not completely lost from the body. Senescence, from both a mechanical (signalling pathways) and a functional point of view, is parallel and complementary to apoptosis in many parameters; apoptosis is another cellular response mechanism to damage. Both apoptosis and senescence are involved in embryonic development and regeneration. Both these mechanisms control cell proliferation and proliferative diseases, including cancer, and are associated with disturbances in these processes. From an evolutionary point of view, these mechanisms are ancient and are present in all multicellular organisms [1].

The transition of a cell to a senescent state or to death through apoptosis may be induced by either internal factors (DNA damage, oxidative stress, disturbances of metabolic systems) or external ‘commands’ that are transmitted mainly through receptors and affect the internal balance of signalling pathways. External signals may be derived from the immediate environment of cells, mainly through paracrine networks of signalling molecules, such as cytokines, chemokines, and growth factors. These molecules are produced, for example, by immune cells as a part of their functions, or senescent cells, as a part of the senescence-associated secretory phenotype (SASP). Such signals may force the surrounding cells into senescence and, in turn, promote local inflammation and attract cells of the immune system [2].

Additionally, there are endocrine systems. It is known that the body is influenced by internal rhythms, diurnal and annual, which are tied to periodic factors such as light and temperature changes, and also react systemically to stressors affecting the body as a whole. All of these functions are mediated through internal hormonal systems, which undoubtedly affect the cell cycle and, accordingly, the mechanisms underlying cell senescence and proliferation.

2. Causes of Cell Senescence

One of the basic causes of senescence is the finite number of divisions initially programmed in cells [3], called Hayflick’s limit. After this number of divisions, the main population of cells in the human body enters an irreversible state of cell cycle arrest called replicative senescence. The underlying mechanism for this is associated with the telomere, that is, the repeating DNA sequence TTAGGG present at the ends of linear chromosomes, protecting the chromosomes from degradation and recombination. Telomeres shorten with each cell cycle due to features of the DNA replication process, such as RNA priming of the lagging strand and the unidirectional action of DNA polymerases. Thus, telomere length is a factor that limits the number of cell divisions [4]. In stem cells and many cancer cells, the enzyme telomerase is expressed; it adds DNA repeats to telomeres, and consequently, cells acquire the ability to divide indefinitely. However, telomerase is not expressed in most cells, and as soon as telomeres become too short, a DNA damage response (DDR) is initiated, leading to the activation of cell cycle inhibitors and resulting in cell senescence [5]. Thus, with age, the body gradually accumulates an increasing number of senescent cells.

However, telomere shortening is not the only cause of senescence. Senescence can also be induced by proliferative stressors such as the over-activation of oncogenes such as Ras [6] and BRAF [7] and the dysfunction of tumour suppressors [8]. Therefore, senescence is a natural defence mechanism against tumours.

Moreover, many factors of an aggressive and stressful nature, particularly reactive oxygen species (ROS), X-rays, ultraviolet radiation, and DNA-damaging agents used in cancer chemotherapy, are capable of initiating DDR and, consequently, senescence. All these factors may lead to DNA damage and induction of senescence through DDR-dependent mechanisms. Senescence may also be activated under conditions of inflammation associated with the excessive release of aggressive compounds by immune cells, such as ROS.

Senescence induces noticeable morphological changes in cells, such as increased volume, smoother shape, and increased intercellular spaces. Cells also demonstrate some features, such as senescence-associated beta-galactosidase (SA-β-Gal) activity, that are usually not observed in normal cells and therefore are used as markers of senescence. Additionally, DNA synthesis is blocked in senescent cells, the foci of DNA damage are visible, satellite DNA appears bloated, and increased expression of some microRNAs is observed. In addition, senescent cells secrete many factors such as cytokines, growth factors, matrix remodelling proteins, proteases, and chemokines, which are collectively referred to as the senescence-associated secretory phenotype (SASP) [9].

The most prominent component of SASP is IL-6, a pleiotropic pro-inflammatory cytokine whose secretion is increased by DDR-dependent and oncogene-induced senescence in a variety of cell types [10][11][12][13]. In senescent cells, increased expressions of IL-1 and IL-8 were observed, and the expressions of IL-6 and IL-8 were upregulated through IL-1 [14]. Most senescent cells also express chemokines, for instance, those belonging to the CCL family [14]. Senescent epithelial cells, endothelial cells, and fibroblasts express high levels of almost all proteins that bind insulin-like growth factors, including IGFBP-2, -3, -4, -5, and -6 [12][15][16], and their regulators, IGFBP-rP1 and IGFBP-rP2 [17][18]. SASP also includes a number of matrix metalloproteases (MMPs), such as MMP-1, -3, and -10 [19][20][21][22][23], and serine proteases and their endogenous inhibitors [24]. In addition, senescent cells release nitric oxide and ROS due to changes in the levels of nitric oxide synthase and superoxide dismutase activity [25][26][27][28][29]. There is evidence that the generation of SASP in senescent cells is associated with the activation of the NF-κB signalling pathway [1], a primary regulator of the proinflammatory response in cells.

Cellular senescence is physiologically normal during embryonic development and in adult organisms. In embryonic tissues, the SASP of senescent cells includes signalling molecules that stimulate morphogenesis. In adult tissues, SASP plays an important role in wound healing, as it suppresses carcinogenesis and stimulates regeneration; however, the underlying mechanisms are different from those in embryonic tissues [2].

Therefore, SASP has a protective function, because it attracts cells of the immune system designed to eliminate damaged and senescent cells and also contributes to the normal processes of inflammation, wound healing, tissue remodelling, and cellular plasticity [30][31][32][33]. On the other hand, these factors can disrupt tissue homeostasis, contributing to the senescence of surrounding cells (paracrine ageing) [34], and chronic inflammation may lead to pathological conditions such as fibrosis and cancer [31]. Long-term exposure to SASP factors may lead to the development of an inflammatory disorder, since it includes a number of pro-inflammatory mediators. As noted above, inflammation is associated with the recruitment of immune cells, the release of aggressive mediators, and stress exposure of the surrounding cells. Long-term chronic exposure to inflammation factors formed during both ‘normal’ chronic inflammation and the accumulation of a large number of senescent cells on the surrounding intact cells may result in stress activation of signalling pathways associated with the arrest of the cell cycle and the initiation of senescence mechanisms.

References

1. Childs, B.G.; Baker, D.J.; Kirkland, J.L.; Campisi, J.; Deursen, J.M. Senescence and Apoptosis: Dueling or Complementary Cell Fates? EMBO Rep. 2014, 15, 1139–1153.
2. Salama, R.; Sadaie, M.; Hoare, M.; Narita, M. Cellular Senescence and Its Effector Programs. Genes Dev. 2014, 28, 99–114.
3. Hayflick, L.; Moorhead, P.S. The Serial Cultivation of Human Diploid Cell Strains. Exp. Cell Res. 1961, 25, 585–621.
4. Bodnar, A.G.; Ouellette, M.; Frolkis, M.; Holt, S.E.; Chiu, C.-P.; Morin, G.B.; Harley, C.B.; Shay, J.W.; Lichtsteiner, S.; Wright, W.E. Extension of Life-Span by Introduction of Telomerase into Normal Human Cells. Science 1998, 279, 349–352.
5. di Fagagna, D.F.; Reaper, P.M.; Clay-Farrace, L.; Fiegler, H.; Carr, P.; von Zglinicki, T.; Saretzki, G.; Carter, N.P.; Jackson, S.P. A DNA Damage Checkpoint Response in Telomere-Initiated Senescence. Nature 2003, 426, 194–198.
6. Di Micco, R.; Fumagalli, M.; Cicalese, A.; Piccinin, S.; Gasparini, P.; Luise, C.; Schurra, C.; Garre’, M.; Giovanni Nuciforo, P.; Bensimon, A.; et al. Oncogene-Induced Senescence Is a DNA Damage Response Triggered by DNA

Hyper-Replication. Nature 2006, 444, 638–642.

7. Michaloglou, C.; Vredeveld, L.C.W.; Soengas, M.S.; Denoyelle, C.; Kuilman, T.; van der Horst, C.M.A.M.; Majoor, D.M.; Shay, J.W.; Mooi, W.J.; Peeper, D.S. BRAFE600-Associated Senescence-like Cell Cycle Arrest of Human Naevi. Nature 2005, 436, 720–724.
8. Alimonti, A.; Nardella, C.; Chen, Z.; Clohessy, J.G.; Carracedo, A.; Trotman, L.C.; Cheng, K.; Varmeh, S.; Kozma, S.C.; Thomas, G.; et al. A Novel Type of Cellular Senescence That Can Be Enhanced in Mouse Models and Human Tumor Xenografts to Suppress Prostate Tumorigenesis. J. Clin. Invest. 2010, 120, 681–693.
9. Wang, Z. Regulation of Cell Cycle Progression by Growth Factor-Induced Cell Signaling. Cells 2021, 10, 3327.
10. Coppé, J.-P.; Patil, C.K.; Rodier, F.; Sun, Y.; Muñoz, D.P.; Goldstein, J.; Nelson, P.S.; Desprez, P.-Y.; Campisi, J. Senescence-Associated Secretory Phenotypes Reveal Cell-Nonautonomous Functions of Oncogenic RAS and the P53 Tumor Suppressor. PLoS Biol. 2008, 6, e301.
11. Lu, S.-Y.; Chang, K.-W.; Liu, C.-J.; Tseng, Y.-H.; Lu, H.-H.; Lee, S.-Y.; Lin, S.-C. Ripe Areca Nut Extract Induces G 1 Phase Arrests and Senescence-Associated Phenotypes in Normal Human Oral Keratinocyte. Carcinogenesis 2006, 27, 1273–1284.
12. Sarkar, D.; Lebedeva, I.V.; Emdad, L.; Kang, D.; Baldwin, A.S.; Fisher, P.B. Human Polynucleotide Phosphorylase (hPNPaseold-35): A Potential Link between Aging and Inflammation. Cancer Res. 2004, 64, 7473–7478.
13. Kuilman, T.; Michaloglou, C.; Vredeveld, L.C.W.; Douma, S.; van Doorn, R.; Desmet, C.J.; Aarden, L.A.; Mooi, W.J.; Peeper, D.S. Oncogene-Induced Senescence Relayed by an Interleukin-Dependent Inflammatory Network. Cell 2008, 133, 1019–1031.
14. Davalos, A.R.; Coppe, J.-P.; Campisi, J.; Desprez, P.-Y. Senescent Cells as a Source of Inflammatory Factors for Tumor Progression. Cancer Metastasis Rev. 2010, 29, 273–283.
15. Wang, S. Characterization Of IGFBP-3, PAI-1 and SPARC MRNA Expression in Senescent Fibroblasts. Mech. Ageing Dev. 1996, 92, 121–132.
16. Grillari, J.; Hohenwarter, O.; Grabherr, R.M.; Katinger, H. Subtractive Hybridization of MRNA from Early Passage and Senescent Endothelial Cells. Exp. Gerontol. 2000, 35, 187–197.
17. López-Bermejo, A.; Buckway, C.K.; Devi, G.R.; Hwa, V.; Plymate, S.R.; Oh, Y.; Rosenfeld, R.G. Characterization of Insulin-Like Growth Factor-Binding Protein-Related Proteins (IGFBP-RPs) 1, 2, and 3 in Human Prostate Epithelial Cells: Potential Roles for IGFBP-RP1 and 2 in Senescence of the Prostatic Epithelium. Endocrinology 2000, 141, 4072–4080.
18. Kim, K.-H.; Park, G.-T.; Lim, Y.-B.; Rue, S.-W.; Jung, J.-C.; Sonn, J.-K.; Bae, Y.-S.; Park, J.-W.; Lee, Y.-S. Expression of Connective Tissue Growth Factor, a Biomarker in Senescence of Human Diploid Fibroblasts, Is up-Regulated by a Transforming Growth Factor-β-Mediated Signaling Pathway. Biochem. Biophys. Res. Commun. 2004, 318, 819–825.
19. Liu, D.; Hornsby, P.J. Senescent Human Fibroblasts Increase the Early Growth of Xenograft Tumors via Matrix Metalloproteinase Secretion. Cancer Res. 2007, 67, 3117–3126.
20. Parrinello, S.; Coppe, J.-P.; Krtolica, A.; Campisi, J. Stromal-Epithelial Interactions in Aging and Cancer: Senescent Fibroblasts Alter Epithelial Cell Differentiation. J. Cell Sci. 2005, 118, 485–496.
21. West, M.D.; Pereira-Smith, O.M.; Smith, J.R. Replicative Senescence of Human Skin Fibroblasts Correlates with a Loss of Regulation and Overexpression of Collagenase Activity. Exp. Cell Res. 1989, 184, 138–147.
22. Millis, A.J.T.; Hoyle, M.; McCue, H.M.; Martini, H. Differential Expression of Metalloproteinase and Tissue Inhibitor of Metalloproteinase Genes in Aged Human Fibroblasts. Exp. Cell Res. 1992, 201, 373–379.
23. Zeng, G.; Millis, A.J.T. Differential Regulation of Collagenase and Stromelysin MRNA in Late Passage Cultures of Human Fibroblasts. Exp. Cell Res. 1996, 222, 150–156.
24. Blasi, F.; Carmeliet, P. UPAR: A Versatile Signalling Orchestrator. Nat. Rev. Mol. Cell Biol. 2002, 3, 932–943.
25. Sato, I.; Morita, I.; Kaji, K.; Ikeda, M.; Nagao, M.; Murota, S. Reduction of Nitric Oxide Producing Activity Associated with in Vitro Aging in Cultured Human Umbilical Vein Endothelial Cell. Biochem. Biophys. Res. Commun. 1993, 195, 1070–1076.
26. Lee, A.C.; Fenster, B.E.; Ito, H.; Takeda, K.; Bae, N.S.; Hirai, T.; Yu, Z.-X.; Ferrans, V.J.; Howard, B.H.; Finkel, T. Ras Proteins Induce Senescence by Altering the Intracellular Levels of Reactive Oxygen Species. J. Biol. Chem. 1999, 274, 7936–7940.
27. van der Loo, B.; Labugger, R.; Skepper, J.N.; Bachschmid, M.; Kilo, J.; Powell, J.M.; Palacios-Callender, M.; Erusalimsky, J.D.; Quaschning, T.; Malinski, T.; et al. Enhanced Peroxynitrite Formation Is Associated with Vascular Aging. J. Exp. Med. 2000, 192, 1731–1744.

28. Macip, S. Inhibition of P21-Mediated ROS Accumulation Can Rescue P21-Induced Senescence. EMBO J. 2002, 21, 2180–2188.
29. Xin, M.-G.; Zhang, J.; Block, E.R.; Patel, J.M. Senescence-Enhanced Oxidative Stress Is Associated with Deficiency of Mitochondrial Cytochrome c Oxidase in Vascular Endothelial Cells. Mech. Ageing Dev. 2003, 124, 911–919.
30. Kang, C.; Xu, Q.; Martin, T.D.; Li, M.Z.; Demaria, M.; Aron, L.; Lu, T.; Yankner, B.A.; Campisi, J.; Elledge, S.J. The DNA Damage Response Induces Inflammation and Senescence by Inhibiting Autophagy of GATA4. Science 2015, 349, aaa5612.
31. Muñoz-Espín, D.; Serrano, M. Cellular Senescence: From Physiology to Pathology. Nat. Rev. Mol. Cell Biol. 2014, 15, 482–496.
32. Mosteiro, L.; Pantoja, C.; Alcazar, N.; Marión, R.M.; Chondronasiou, D.; Rovira, M.; Fernandez-Marcos, P.J.; Muñoz-Martin, M.; Blanco-Aparicio, C.; Pastor, J.; et al. Tissue Damage and Senescence Provide Critical Signals for Cellular Reprogramming in Vivo. Science 2016, 354, aaf4445.
33. Ritschka, B.; Storer, M.; Mas, A.; Heinzmann, F.; Ortells, M.C.; Morton, J.P.; Sansom, O.J.; Zender, L.; Keyes, W.M. The Senescence-Associated Secretory Phenotype Induces Cellular Plasticity and Tissue Regeneration. Genes Dev. 2017, 31, 172–183.
34. Acosta, J.C.; Banito, A.; Wuestefeld, T.; Georgilis, A.; Janich, P.; Morton, J.P.; Athineos, D.; Kang, T.-W.; Lasitschka, F.; Andrulis, M.; et al. A Complex Secretory Program Orchestrated by the Inflammasome Controls Paracrine Senescence. Nat. Cell Biol. 2013, 15, 978–990.
