MicroRNA controls of cellular senescence

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Cellular senescence is a state of permanent cell-cycle arrest triggered by different internal and external stimuli. This phenomenon is considered to be both beneficial and detrimental depending on the cell types and biological contexts. During normal embryonic development and after tissue injury, cellular senescence is critical for tissue remodeling. In addition, this process is useful for arresting growth of tumor cells, particularly during early onset of tumorigenesis. However, accumulation of senescent cells decreases tissue regenerative capabilities and induces inflammation, which is responsible for cancer and organismal aging. Therefore, cellular senescence has to be tightly regulated, and dysregulation might lead to the aging and human diseases. Among many regulators of cellular senescence, in this review, I will focus on microRNAs, small non-coding RNAs playing critical roles in diverse biological events including cellular senescence. [BMB Reports 2018; 51(10): 493-499]

INTRODUCTION

Over half a century ago, cellular senescence was first characterized as the finite replicative potential in cultured human fibroblasts by Leonard Hayflick (1, 2), which is known as replicative senescence. Since then, extensive studies have broadened the concept of cellular senescence, an irreversible cell-cycle arrest in response to a variety of internal and external stress signals (3-5). Along with the replicative senescence, senescence caused by diverse stressors is collectively known as premature senescence (5). However, depending on different stimuli the cells encounter, the premature and/or induced senescence can be classified into different types (6). Telomere shortening generated by repeated DNA replication is mainly responsible for replicative senescence (7, 8). DNA damage induced by ionizing radiation (IR), ultraviolet (UV), and other oxidative agents resulting in a double-stranded DNA break are potent inducers of DNA damage-induced senescence (9, 10). Activation of oncopgenes or inactivation of tumor suppressors is a major cause of oncogene-induced senescence (OIS) (7, 10, 11). In addition, oxidative stress and reactive oxygen species (ROS) can triggers oxidative stress-induced senescence (12). Recently, it has been reported that mitochondrial dysfunction-associated senescence with distinct secretory phenotypes is caused by dysfunctional mitochondria (13). However, in some cases, the classification of cellular senescence is ambiguous because of the complex causes of the events and overlapping effector pathways.

Phenotypically, senescent cells exhibit enlarged and flattened shapes that are in part determined by activation of the mTOR pathway (14). The cellular senescence is also characterized by increased lysosomal components, where the activity of the lysosomal enzyme, such as senescence-associated β-galactosidase (SA-β-gal), is commonly used as a marker for senescence (15). Alteration in chromatic structures, such as senescence-associated heterochromatin foci (SAHF), which are specialized domains of heterochromatin, is often associated with senescent cells. At the molecular level, tumor-suppressor networks, namely, p53-p21 and p16 INK4A -retinoblastoma (p16-pRB) pathways, are commonly activated in the senescence program (16). However, no single characteristic is a specific hallmark of cellular senescence, and not all senescent cells show the aforementioned features of senescence.

Accumulation of evidence suggests that cellular senescence has both helpful and deleterious functions (10, 17). During normal embryogenesis, senescence participates in morphogenesis and tissue remodeling (10). In response to a fetal HLA-G signal, nearby natural killer (NK) cells enter senescent state which continuously secretes factors for maternal vascular remodeling (18). Developmentally programmed senescence responsible for morphogenesis is also found throughout embryonic development at multiple sites, such as mesonephros, endolymphatic sac (19), and the apical ectodermal ridge (20). In addition to developmental functions, senescent cells help restrict tumor progression (21) and fibrosis in the liver, heart, and kidneys (10) and promote wound healing (22, 23). However, accumulation of senescent cells has detrimental effects as well. They can trigger aging and age-related pathological processes, such as tumorigenesis (24) and metabolic diseases (10). For example, some senescence-
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Table 1. miRNAs differentially expressed in senescent cells

| Profiling technology | Differentially expressed miRNAs in senescent cells | Reference |
|----------------------|--------------------------------------------------|-----------|
| miRNA microarray (MMchip) | Up: let-7c, let-7d, miR-10b, miR-26a, miR-34a, miR-106b, miR-136, miR-137, miR-144, miR-195, miR-200b, miR-363, miR-373, miR-377, miR-432, miR-485-5p, miR-517, miR-609, miR-624, miR-633, miR-638, miR-663<br>Down: miR-32, miR-147, miR-196b, miR-197, miR-218, miR-365, miR-425, miR-512-5p, miR-517a, miR-619 | 38 |
| miRNome array | Up: miR-34c-3p, miR-122, miR-124, miR-129-3p, miR-146b-3p, miR-203, miR-216b, miR-219-3p, miR-372, miR-431, miR-432, miR-451, miR-492, miR-499-3p, miR-513a-5p, miR-513b, miR-519a, miR-519b-3p, miR-519c-3p, miR-548b-3p, miR-548k, miR-548p, miR-561, miR-572, miR-619, miR-641, miR-658, miR-663, miR-874, miR-890, miR-944, miR-1180, miR-1185, miR-1204, miR-1225-3p, miR-1244, miR-1248, miR-1250, miR-1255b, miR-1259, miR-1270, miR-1271, miR-1273, miR-1279, miR-1282, miR-1284, miR-1286, miR-1289, miR-1291, miR-1303, miR-1305, miR-1322, miR-1357<br>Down: let-7a/b/c/d/e/f/g, miR-7, miR-10a/b, miR-15a, miR-16-1/b, miR-17, miR-20a, miR-32, miR-92-1a/b, miR-93a, miR-106a/b, miR-123b, miR-135b, miR-143, miR-145, miR-155, miR-195, miR-217b, miR-218a, miR-232, miR-424-2, miR-450-2b, miR-483 | 39 |
| miRNA array | Up: miR-22, miR-27, miR-29b, miR-30a/c, miR-34a, miR-101b, miR-103, miR-106a, miR-123, miR-127, miR-128a, miR-129-134, miR-132, miR-139, miR-219, miR-259, miR-323, miR-337, miR-340, miR-376a, miR-376b, miR-379, miR-380-3p, miR-382, miR-410, miR-431, miR-432, miR-433, miR-486, miR-493, miR-494, miR-496, miR-516-3p<br>Down: miR-7, miR-15a/b, miR-16-1/b, miR-17-19b, miR-20a/b, miR-25-29b, miR-30c-1, miR-32, miR-92-1a/b, miR-93a, miR-106a/b, miR-123b, miR-135b, miR-143, miR-145, miR-155, miR-195, miR-217b, miR-218a, miR-224, miR-424-2, miR-450-2b, miR-483 | 40 |
| Deep sequencing | Up: miR-122, miR-126, miR-129-3p, miR-129-5p, miR-184, miR-217, miR-323b-3p, miR-375, miR-432, miR-433, miR-439, miR-491-5p, miR-496, miR-539, miR-584, miR-668, miR-765, miR-1197, miR-1246, miR-1274a/b, miR-1275, miR-1290, miR-1356, miR-379, miR-1287<br>Down: miR-15a/b, miR-16-1/b, miR-17-19b, miR-20a/b, miR-25-29b, miR-30c-1, miR-32, miR-92-1a/b, miR-93a, miR-106a/b, miR-123b, miR-135b, miR-143, miR-145, miR-155, miR-195, miR-217b, miR-218a, miR-224, miR-424-2, miR-450-2b, miR-483 | 41 |

*miRNAs which show more than five-fold changes in senescent cells are listed. A complete list of differentially expressed miRNAs is found in Ref 41.*

Several studies reported the miRNA expression profiles during cellular senescence by various profiling technologies (Table 1).
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Maes et al. reported the expression profiles of 462 miRNAs using a human miRNA microarray (MMchip) in replicative and premature senescent human fibroblasts along with quiescence cells (38). Depending on the growth-arrest conditions, a subset of miRNAs is specific or common in two or three states (38). Among those, miR-10b, miR-34a, miR-373, miR-377, miR-624, miR-633, miR-638, and miR-663 are commonly upregulated in three growth-arrested cells (38). Using miRNome arrays, which are based on qPCR analysis, the Abdelmohsen group validated that there are a subset of miRNAs notably up- or down-regulated in senescent human fibroblasts (39). Among those, miR-519, a tumor-suppressor miRNA, is highly expressed in senescent cells, and when overexpressed in either young fibroblasts or HeLa cells, it indeed triggered senescence (39). The Wang group performed miRNA microarray analysis with replicative, IR, or busulfan (BU)-induced senescent human fibroblasts (40). They showed that eight miRNAs are differentially expressed in both replicative and induced senescent cells: miR-152, miR-410, miR-431, and miR-493 are up-regulated, and miR-15a, miR-20a, miR-25, and miR-155 are down-regulated (40). Knockdown or overexpression of these miRNAs revealed their functions during senescence. Using deep sequencing analysis, Dhahbi et al. discovered miRNAs differentially expressed in young and senescent human fibroblasts (41). They reported that 141 miRNAs were upregulated and 131 miRNAs were downregulated upon senescence. In addition to miRNAs already known to be associated with cellular senescence, there are novel miRNAs (e.g., miR-432 and miR-145) differentially expressed during senescence. The lists of miRNAs during senescence may disagree because of the different cell types or senescence models or technologies adopted.

miRNAs IMPLICATED IN KEY SENESCENCE PATHWAYS

In addition to the global profiling experiments, the role of individual miRNAs during senescence has been investigated by numerous functional studies. I will focus on two major senescence signaling pathways, namely, p53-p21 and/or p16-pRB to review the functions of senescence-associated miRNAs (Fig. 1).

miRNAs associated with the p53-p21 axis

miRNAs directly regulate p53: The p53 protein, a key regulator of the G1/S and G2/M checkpoints, activates transcription of numerous genes participating in the control of the cell cycle, such as p21. There are miRNAs that directly and/or indirectly regulate p53, which indicates elaborate controls of a crucial tumor suppressor. miR-504 (42), miR-125b (43), miR-25, and miR-30d (44) directly bind to and suppress p53. Different groups independently showed that ectopic expression of these miRNAs decreases p53 expression and several cellular functions, including p53-mediated cell-cycle arrest, suggesting their role in senescence suppression.

miRNAs indirectly regulate p53 through p53 suppressors:

Several miRNAs negatively regulate the suppressors of p53, thereby inducing senescence. For instance, miR-192, miR-194, miR-215 (45), and miR-605 (46) indirectly upregulate p53 through downregulation of the murine double-minute clone 2 (MDM2), an oncogene suppressing p53 expression. Notably, this subset of miRNAs is regulated by p53, thereby constituting a positive feedback loop (45, 46). Another regulatory loop between miRNAs, a target gene, and p53 can be found in an example of miR-34a, one of the most-studied miRNAs in this network. Specifically, miR-34a promotes cellular senescence by suppressing the silent-mating type information regulation 2 homologue 1 (SIRT1), a deacetylase that negatively regulates p53 and stress-response pathways (47-52). Along with miR-34a, miR-22 (53, 54), miR-138 (55), miR-181a/b (55), miR-217 (56), and miR-449 (57) reduce SIRT1 expression, thereby increasing p53 expression and senescence in various cancers and normal cells.

The Asgary group reported that miR-195 is overexpressed in senescent stem cells and that silencing miR-195 in old MSCs increases the expression of telomerase reverse transcriptase (TERT) and SIRT1 and increases p53 levels (58). The mediator...
of DNA damage checkpoint 1 (MDC1), a crucial component of the DNA damage response (DDR) machinery (59) is another regulatory point by miRNAs during senescence. It is reported that miR-22 directly suppresses MDC1 and hence promotes premature senescence (60).

miRNAs regulate p21: Multiple miRNAs directly downregulate p21 and therefore suppress senescence. Borgdorff et al. performed miRNA screening experiments and reported that 28 miRNAs prevented RASt13-induced senescence by inhibiting p21 expression in human mammary epithelial cells: miR-106b family members, miR-302a/b/c/d, miR-512-3p, and miR-515-3p (61). This is consistent with the earlier finding that downregulation of miR-106a contributed to the upregulation of p21 in senescent human fibroblasts and trabecular meshwork cells (62). In a colon-carcinoma cell line, miR-20a downmodulates p21 expression and abrogates TGF-β-induced G1/S arrest (63). miR-663, which is more abundantly expressed in senescent cells (38, 39), directly targets p21 and inhibits the G1/S transition in nasopharyngeal carcinoma cells (64). As mentioned earlier, miR-519 is highly abundant in senescent cells (39). At the molecular level, miR-519 promotes growth inhibition partially by increasing DNA damage response and decreasing cytosolic calcium status, which all in turn elevate the p21 expression (65). Taken together, some miRNAs exert their effect on senescence by targeting multiple p21-inducing pathways.

miRNAs associated with the p16-pRB pathway miRNAs directly regulate p16: The other core converged pathways during cellular senescence is p16-pRB (66, 67). The p16, the prototypical member of cyclin-dependent inhibitor, is encoded by the CDKN2A gene in humans (68, 69). Because of its crucial role in the cell cycle, regulation of p16 is complex and involves interactions with numerous factors. Lal et al. reported that decreased miR-24 expression is associated with increased p16 levels with replicative senescence (70). Several groups demonstrated that miR-24 directly binds to and suppresses p16 translation in human cells, different tumor lines, and a disease model, such as osteoarthritis (70-72).

miRNAs indirectly regulate p16: Some miRNAs indirectly regulate p16 and hence affect cellular senescence. Interestingly, several miRNAs control polycomb repressive complexes (PRC1 and PRC2). Amongst other diverse cellular processes, these epigenetic regulators influence senescence in part by silencing the INK4/ARF locus, where p16 is located. For instance, the miR-9, miR-125, and miR-181 families modulate CBX7 (chromobox homologue 7), one of the components of PRC1, which in turn induces senescence in a p16-dependent manner (73). Other polycomb group (PcG) proteins, such as BMI1 (B cell-specific Moloney murine leukemia virus integration site 1, polycomb ring finger oncogene) and EZH2 (enhancer of zeste homologue 2) are also targeted by miRNAs, thereby affecting the senescence state. BMI1 is repressed by miR-141, which in turn promotes senescence in human fibroblasts (74). The same protein is also regulated by miR-128a with increased intracellular ROS level and senescence in medulloblastoma cancer cells (75). miR-138 induces senescence through EZH2 repression in renal-cell carcinoma (76). This type of regulation between miRNAs with PcG and senescence are all dependent on p16 overexpression. More recently, a systematic approach combining miRNA screening and miRNA profiling revealed a more complex association of miRNAs, epigenetic regulators, and a p16 pathway (77). miR-26b, miR-181a, miR-210, and miR-424 directly suppress diverse PcG proteins, such as CBX7, EED (embryonic ectoderm development), EZH2, and Suz12 (suppressor of zeste 12 homologue), following increased levels of p16 and senescence (77).

Additionally, forced expression of miR-335 is associated with senescence phenotypes, including augmented p16 levels in hMSCs, with reduction of therapeutic potential (78). Interestingly, a loss-of-function screening assay identified miR-335 as a tumor suppressor involved in senescence by targeting p16, pRB, p21, and CARF (collaborate of ARF) (79). Not surprisingly, in some cases, a battery of miRNAs (e.g., miR-15b, miR-24, miR-25, and miR-141) all together represses M KK4 (mitogen-activated protein kinase (MAPK) kinase 4) and decreases p16 protein levels and senescence in human fibroblasts (80).

miRNAs regulate pRB: It has been reported that expression of two miRNA families, miR-29 and miR-30, is induced during senescence in a pRB-dependent mode (81). Martinez et al. demonstrated that these miRNAs exert their effect by directly targeting the B-Myb oncogene, which indicates their role in Rb-driven cellular senescence (81). Interestingly, downregulation of B-Myb is also associated with senescence through the ROS-mediated p53/p21 axis, both in vivo and in vitro (82), which suggests the integration of senescence regulation.

In prostate cancer cells, miR-449a directly represses the cyclin D1 (CCND1) gene, a regulator of Rb activity, which sequentially modulates growth and senescence in an Rb-dependent mechanism (83). Similar regulation of miR-449a within the Rb regulatory network and senescence has been shown in human lung-cancer cells through targeting E2F3, a key regulator of G1/S transition (84, 85). In addition, the E2F3 is a downstream target of miR-203 in human melanoma cells (86). Interestingly, miR-203 represses ZBP-89 as well but silencing of E2F3, not ZBP-89, contributes to the induction of senescence phenotypes. Consistent with this result, E2F3 overexpression rescued melanoma cells from senescence induced by miR-203 (86).

CONCLUSIONS AND PERSPECTIVES

Senescence is a highly heterogeneous cellular process. It is becoming increasingly evident that regulation of a single factor by an individual regulator can hardly define how senescence is initiated and maintained. Therefore, it is crucial to
understand specific and more general regulatory mechanisms at many levels. miRNAs are one of the suitable regulators in this process, because they can simultaneously alter levels of multiple genes and pathways. Analyzing global miRNA expression profiles of different senescence states or comparing other growth-arrest conditions, such as quiescence, would be a primary approach to understanding the molecular constitutions of cellular senescence. Alternatively, miRNA functions can be studied more globally by removing all miRNAs in the system, by deleting genes involved in miRNA biogenesis, namely, Dicer or DGR8. Loss of miRNA biogenesis by ablating the Dicer gene in mouse fibroblasts induces p19AS-p53 levels and senescence (87). Similarly, DGR8 loss triggers cellular senescence in both murine and human fibroblasts in a p21-dependent manner (88). Finally, as described above, numerous studies performed on individual miRNAs also greatly expand our knowledge of senescence controls. In many cases, the feedback loop between miRNAs and key nodes of regulatory pathways are reported, which further indicate the complex regulation of this process. Additional studies are now needed to develop strategies to manipulate and deliver therapeutic miRNA to reinforce or prevent the senescent state, depending on the physiological outcome one might expect.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

REFERENCES

1. Hayflick L and Moorhead PS (1961) The serial cultivation of human diploid cell strains. Exp Cell Res 25, 585-621
2. Hayflick L (1965) The Limited In Vitro Lifetime of Human Diploid Cell Strains. Exp Cell Res 37, 614-636
3. Campisi J and d'Adda di Fagagna F (2007) Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol 8, 343-352
4. Collado M, Blasco MA and Serrano M (2007) Cellular senescence in cancer and aging. Cell 130, 223-233
5. Kuijman T, Michaloglou C, Mooi WJ and Peeper DS (2010) The essence of senescence. Genes Dev 24, 2463-2479
6. Hernandez-Segura A, Nehme J and Demaria M (2018) Hallmarks of Cellular Senescence. Trends Cell Biol 28, 436-453
7. Sharpless NE and Sherr CJ (2015) Forging a signature of in vivo senescence. Nat Rev Cancer 15, 397-408
8. Herbig U, Jobling WA, Chen BP, Chua DJ and Sedivy JM (2004) Telomere shortening triggers senescence of human cells through a pathway involving ATM, p53, and p21(CIP1), but not p16(INK4a). Mol Cell 14, 501-513
9. Petrova NV, Velichko AK, Razzin SV and Kantidze OL (2016) Small molecule compounds that induce cellular senescence. Aging Cell 15, 999-1017
10. Munoz-Espin D and Serrano M (2014) Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol 15, 482-496
11. Serrano M, Lin AW, McCurrach ME, Beach D and Lowe SW (1997) Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. Cell 88, 593-602
12. Lu T and Finkel T (2008) Free radicals and senescence. Exp Cell Res 314, 1918-1922
13. Wiley CD, Velarde MC, Lecot P et al (2016) Mitochondrial Dysfunction Induces Senescence with a Distinct Secretory Phenotype. Cell Metab 23, 303-314
14. Bent EH, Gilbert LA and Hemann MT (2016) A senescence secretory switch mediated by P3K/AKT/mTOR activation controls chemoprotective endothelial secretory responses. Genes Dev 30, 1811-1821
15. Lee BY, Han JA, Im JS et al (2006) Senescence-associated beta-galactosidase is lysosomal beta-galactosidase. Aging Cell 5, 187-195
16. Lowe SW, Cepero E and Evan G (2004) Intrinsic tumour suppression. Nature 432, 307-315
17. Childs BG, Baker DJ, Kirkland JL, Campisi J and van Deursen JM (2014) Senescence and apoptosis: dueling or complementary cell fates? EMBO Rep 15, 1139-1153
18. Rajagopalan S and Long EO (2012) Cellular senescence secretory switch mediated by PI3K/AKT/mTOR. Cell Metab 23, 303-314
19. Munoz-Espin D, Canamero M, Muravev A et al. (2013) Programmed cell senescence during mammalian embryonic development. Cell 155, 1104-1118
20. Storer M, Mas A, Robert-Moreno A et al (2013) Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell 155, 1119-1130
21. Collado M and Serrano M (2010) Senescence in tumours: evidence from mice and humans. Nat Rev Cancer 10, 51-57
22. Jun H and Lau LF (2010) Cellular senescence controls fibrosis in wound healing. Aging (Albany NY) 2, 627-631
23. Kong X, Feng D, Wang H et al (2012) Interleukin-22 induces hepatic stellate cell senescence and restricts liver fibrosis in mice. Hepatology 56, 1150-1159
24. Lecot P, Almirall F, Desprez PY, Campisi J and Wiley C (2016) Context-dependent effects of cellular senescence in cancer development. Br J Cancer 114, 1180-1184
25. Coppe JP, Patil CK, Rodier F et al (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6, 2853-2868
26. Kuijman T, Michaloglou C, Vredelev LC et al (2008) Oncogene-induced senescence relayed by an interleukin-
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dependent inflammatory network. Cell 133, 1019-1031
27. Davalos AR, Coppe JP, Campisi J and Desprez PY (2010) Senescent cells as a source of inflammatory factors for tumor progression. Cancer Metastasis Rev 29, 273-283
28. Turinetto V, Vitale E and Giachino C (2016) Senescence in Human Mesenchymal Stem Cells: Functional Changes and Implications in Stem Cell-Based Therapy. Int J Mol Sci 17, pii. E1164
29. Banfi A, Muraglia A, Dozin B, Mastrogiacomo M, Cancedda R and Quarto R (2000) Proliferation kinetics and differentiation potential of ex vivo expanded human bone marrow stromal cells: Implications for their use in cell therapy. Exp Hematol 28, 707-715
30. Cheng H, Qiu L, Ma J et al (2011) Replicative senescence of human bone marrow and umbilical cord derived mesenchymal stem cells and their differentiation to adipocytes and osteoblasts. Mol Biol Rep 38, 5161-5168
31. Kim M, Kim C, Choi YS, Kim M, Park C and Suh Y (2012) Age-related alterations in mesenchymal stem cells related to shift in differentiation from osteogenic to adipogenic potential: implication to age-associated bone diseases and defects. Mech Ageing Dev 133, 215-225
32. Sepulveda JC, Tome M, Fernandez ME et al (2014) Cell senescence abrogates the therapeutic potential of human mesenchymal stem cells in the lethal endotoxemia model. Stem Cells 32, 1865-1877
33. Geissler S, Textor M, Kuhnisch J et al (2012) Deep sequencing reveals novel and conserved microRNAs and regulation of microRNA expression during cell senescence. PLoS One 7, e52700
34. Bartel DP (2009) MicroRNAs: target recognition and regulatory functions. Cell 136, 215-233
35. Suh N and Blelloch R (2011) Small RNAs in early states in WI-38 human fibroblasts. J Cell Physiol 221, 109-119
36. Farh KK, Grimson A, Jan C et al (2005) The widespread impact of mammalian MicroRNAs on mRNA repression and evolution. Science 310, 1817-1821
37. Subramanyam D and Blelloch R (2011) From microRNAs to targets: pathway discovery in cell fate transitions. Curr Opin Genet Dev 21, 498-503
38. Maes OC, Sarojini H and Wang E (2009) Stepwise up-regulation of microRNA expression levels from replicative to reversible and irreversible growth arrest states in WI-38 human fibroblasts. J Cell Physiol 221, 109-119
39. Marasa BS, Srikantan S, Martindale JL et al (2010) MicroRNA profiling in human diploid fibroblasts uncovers miR-519 role in replicative senescence. Aging (Albany NY) 2, 333-343
40. Wang Y, Scheiber MN, Neumann C, Calin GA and Zhou D (2011) MicroRNA regulation of ionizing radiation-induced premature senescence. Int J Radiat Oncol Biol Phys 81, 839-848
41. Dhahtbi JM, Atamna H, Boffelli D, Magis W, Spindler SR and Martin DI (2011) Deep sequencing reveals novel microRNAs and regulation of microRNA expression during cell senescence. PLoS One 6, e20509
42. Hu W, Chan CS, Wu R et al (2010) Negative regulation of tumor suppressor p53 by microRNA mir-504. Mol Cell 38, 689-699
43. Le MT, Teh C, Shyh-Chang N et al (2009) MicroRNA-125b is a novel negative regulator of p53. Genes Dev 23, 862-876
44. Kumar M, Lu Z, Takwi AA et al (2011) Negative regulation of the tumor suppressor p53 gene by microRNAs. Oncogene 30, 843-853
45. Pichiorri F, Suh SS, Rocci A et al (2010) Downregulation of p53-inducible microRNAs 192, 194, and 215 impairs the p53/MDM2 autoregulatory loop in multiple myeloma development. Cancer Cell 18, 367-381
46. Xiao J, Lin H, Luo X, Luo X and Wang Z (2011) miR-605 joins p53 network to form a p53:miR-605:MDM2 positive feedback loop in response to stress. EMBO J 30, 5021
47. Luo J, Nikolaev AY, Imai S et al (2013) Negative control of p53 by Sirzalpaha promotes cell survival under stress. Cell 107, 137-148
48. Zhao T, Li J and Chen AF (2010) MicroRNA-34a induces endothelial progenitor cell senescence and impedes its angiogenesis via suppressing silent information regulator 1. Am J Physiol Endocrinol Metab 299, E110-116
49. Ito T, Yagi S and Yamakuchi M (2010) MicroRNA-34a regulation of endothelial senescence. Biochem Biophys Res Commun 398, 735-740
50. Yamakuchi M, Ferlito M and Lowenstein CJ (2008) miR-34a repression of SIRT1 regulates apoptosis. Proc Natl Acad Sci U S A 105, 13421-13426
51. Cui H, Ge J, Xie N et al (2017) miR-335 and miR-34a Promote renal senescence by suppressing mitochondrial antioxidative enzymes. J Am Soc Nephrol 22, 1252-1261
52. Bai XY, Ma Y, Ding R, Fu B, Shi S and Chen XM (2011) miR-335 and miR-34a repression of SIRT1 regulates apoptosis. Proc Natl Acad Sci U S A 108, 15378-15383
53. Jazbutyte V, Fiedler J, Knetz S et al (2013) MicroRNA-22 increases senescence and activates cardiac fibroblasts in the aging heart. Age (Dordr) 35, 747-762
54. Xu D, Takeshita F, Hino Y et al (2011) miR-22 represses cancer progression by inducing cellular senescence. J Cell Biol 193, 409-424
55. Rivetti di Val Cervo P, Lena AM, Nicoloso M et al (2012) MicroRNA-22 regulates endothelial cell senescence and suppresses DNA repair and promotes genomic instability. J Pathol 228, 152-162
56. Menghini R, Casagrande V, Cardellini M et al (2009) MicroRNA-217 modulates endothelial cell senescence via suppressing mitochondrial antioxidative enzymes. J Cell Sci 122, 1373-1383
57. Zambute V, Fiedler J, Knetz S et al (2013) MicroRNA-22 increases senescence and activates cardiac fibroblasts in the aging heart. Age (Dordr) 35, 747-762
58. Xu D, Takeshita F, Hino Y et al (2011) miR-22 represses cancer progression by inducing cellular senescence. J Cell Biol 193, 409-424
59. Rivetti di Val Cervo P, Lena AM, Nicoloso M et al (2012) MicroRNA-22 decreases angiogenesis and impairs angiogenesis via suppressing silent information regulator 1. Circulation 120, 1524-1532
60. Bou Kheir T, Futoma-Kazmierzak E, Jacobsen A et al (2011) miR-449 inhibits cell proliferation and is down-regulated in gastric cancer. Mol Cancer 10, 29
61. Okada M, Kim HW, Matsu-ura K, Wang YG, Xu M and Ashraf M (2016) Abrogation of Age-Induced MicroRNA-195 Feedback Loop in Response to Stress. Mol Cell 60, 1291-1300
62. Ashraf M (2016) Abrogation of Age-Induced MicroRNA-195 Feedback Loop in Response to Stress. Mol Cell 60, 1291-1300
63. Menghini R, Casagrande V, Cardellini M et al (2009) MicroRNA-217 modulates endothelial cell senescence via suppressing mitochondrial antioxidative enzymes. J Cell Sci 122, 1373-1383
64. Zambute V, Fiedler J, Knetz S et al (2013) MicroRNA-22 increases senescence and activates cardiac fibroblasts in the aging heart. Age (Dordr) 35, 747-762
65. Xu D, Takeshita F, Hino Y et al (2011) microRNA-22 represses cancer progression by inducing cellular senescence. J Cell Biol 193, 409-424
66. Rivetti di Val Cervo P, Lena AM, Nicoloso M et al (2012) MicroRNA-22 decreases angiogenesis and impairs angiogenesis via suppressing silent information regulator 1. Circulation 120, 1524-1532
67. Bou Kheir T, Futoma-Kazmierzak E, Jacobsen A et al (2011) microRNA-449 inhibits cell proliferation and is down-regulated in gastric cancer. Mol Cancer 10, 29
68. Okada M, Kim HW, Matsu-ura K, Wang YG, Xu M and Ashraf M (2016) Abrogation of Age-Induced MicroRNA-195 Feedback Loop in Response to Stress. Mol Cell 60, 1291-1300
69. Ashraf M (2016) Abrogation of Age-Induced MicroRNA-195 Feedback Loop in Response to Stress. Mol Cell 60, 1291-1300
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61. Borgdorff V, Leonart ME, Bishop CL et al (2010) Multiple microRNAs rescue from Ras-induced senescence by inhibiting p21(Waf1/Cip1). Oncogene 29, 2262-2271

62. Li G, Luna C, Qiu J, Epstein DL and Gonzalez P (2009) Alterations in microRNA expression in stress-induced cellular senescence. Mech Ageing Dev 130, 731-741

63. Sokolova V, Fiorino A, Zoni E et al (2015) The Effects of miR-20a on p21: Two Mechanisms Blocking Growth Arrest in TGF-beta-Responsive Colon Carcinoma. J Cell Physiol 230, 3105-3114

64. Yi C, Wang Q, Wang et al (2012) MiR-663, a microRNA targeting p21(WAF1/CIP1), promotes the proliferation and tumorigenesis of nasopharyngeal carcinoma. Oncogene 31, 4421-4433

65. Abdelmohsen K, Srikantan S, Tominaga K et al (2012) Growth inhibition by miR-519 via multiple p21-inducing pathways. Mol Cell Biol 32, 2530-2548

66. Alcorta DA, Xiong Y, Phelps D, Hannon G, Beach D and Barrett JC (1996) Involvement of the cyclin-dependent kinase inhibitor p16(INK4a) in replicative senescence of normal human fibroblasts. Proc Natl Acad Sci U S A 93, 13742-13747

67. Di Micco R, Fumagalli M, Cicalese A et al (2006) Oncogene-induced senescence is a DNA damage response triggered by DNA hyper-replication. Nature 444, 638-642

68. Nobori T, Miura K, Wu DJ, Lois A, Takabayashi K and Carson DA (1994) Deletions of the cyclin-dependent kinase-4 inhibitor gene in multiple human cancers. Nature 368, 753-756

69. Stone S, Jiang P, Dayananth P et al (1995) Complex structure and regulation of the P16 (MTS1) locus. Cancer Res 55, 2988-2994

70. Lal A, Kim HH, Abdelmohsen K et al (2008) p16(INK4a) expression is suppressed by miR-24. PLoS One 3, e1864

71. Giglio S, Cirombella R, Amodeo R, Portaro L, Lavra L and Vecchione A (2013) MicroRNA miR-24 promotes cell proliferation by targeting the CDKs inhibitors p27Kip1 and p16INK4a. J Cell Physiol 228, 2015-2023

72. Philipot D, Guerit D, Platano D et al (2014) p16INK4a and its regulator miR-24 link senescence and chondrocyte terminal differentiation-associated matrix remodeling in osteoarthritis. Arthritis Res Ther 16, R58

73. O’Loghlen A, Brookes S, Martin N, Rapisarda V, Peters G and Gil J (2015) CBX7 and miR-9 are part of an autoregulatory loop controlling p16INK4a (4a). Aging Cell 14, 1113-1121

74. Dimri M, Carroll JD, Cho JH and Dimri GP (2013) microRNA-141 regulates Bmi1 expression and induces senescence in human diploid fibroblasts. Cell Cycle 12, 3537-3546

75. Venkataraman S, Alimova I, Fan R, Harris P, Foreman N and Vithakaran R (2010) MicroRNA 128a increases intracellular ROS level by targeting Bmi-1 and inhibits medulloblastoma cancer cell growth by promoting senescence. PLoS One 5, e10748

76. Liang J, Zhang Y, Jiang G et al (2013) MiR-138 induces renal carcinoma cell senescence by targeting EZH2 and is downregulated in human clear cell renal cell carcinoma. Oncol Res 21, 83-91

77. Overhoff MG, Garbe JC, Koh J, Stamper MR, Beach DH and Bishop CL (2014) Cellular senescence mediated by p16INK4A-coupled miRNA pathways. Nucleic Acids Res 42, 1606-1618

78. Tome M, Sepulveda JC, Delgado M et al (2014) miR-335 correlates with senescence/aging in human mesenchymal stem cells and inhibits their therapeutic actions through inhibition of AP-1 activity. Stem Cells 32, 2229-2244

79. Yu Y, Gao R, Kaul Z et al (2016) Loss-of-function screening to identify miRNAs involved in senescence: tumor suppressor activity of miRNA-335 and its new target CARF. Sci Rep 6, 30185

80. Marasa BS, Srikantan S, Masuda K et al (2009) Increased MKK4 abundance with replicative senescence is linked to the joint reduction of multiple microRNAs. Sci Signal 2, ra69

81. Martinez J, Cazalla D, Almenet A, Bi F, Zilinskas R and Maixent C (2011) miR-29 and miR-30 regulate B-Myb expression during cellular senescence. Proc Natl Acad Sci U S A 108, 522-527

82. Zhou Z, Yin Y, Chang Q, Sun G, Lin J and Dai Y (2017) Downregulation of B-myb promotes senescence via the ROS-mediated p53/p21 pathway, in vascular endothelial cells. Cell Prolif 50, e12319

83. Noonan E, Place R, Basak S, Pookot D and Li LC (2010) miR-449a causes Rb-dependent cell cycle arrest and senescence in prostate cancer cells. Oncotarget 1, 349-358

84. Humbert PO, Verona R, Trimbarchi JM, Rogers C, Dandapani S and Lees JA (2000) E2F3 is critical for normal cellular proliferation. Genes Dev 14, 690-703

85. Ren XS, Yin MH, Zhang X et al (2014) Tumor-suppressive microRNA-449a induces growth arrest and senescence by targeting E2F3 in human lung cancer cells. Cancer Lett 344, 195-203

86. Noguchi S, Mori T, Otsuka Y et al (2012) Anti-oncogenic microRNA-203 induces senescence by targeting E2F3 protein in human melanoma cells. J Biol Chem 287, 11769-11777

87. Mutisya K, Zhu Z, Hutvagner G et al (2008) Loss of miRNA biogenesis induces p19Arf-p53 signaling and senescence in primary cells. J Cell Biol 181, 1055-1063

88. Gomez-Cabello D, Adrados I, Gamarra D et al (2013) microRNA biogenesis induces cellular senescence in primary fibroblasts. Aging Cell 12, 923-931