Reviews

Stress factor – dependent differences in molecular mechanisms of premature cell senescence

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Cell senescence is an established cell stress response in the form of a permanent proliferation arrest accompanied by a complex phenotype. Senescent cells share several crucial features, such as lack of DNA synthesis, increased senescence-associated β-galactosidase activity and upregulation of cyclin-dependent kinase inhibitors. Most of these universal senescence markers are indicative not only for cell senescence but for other types of growth arrest as well. Along with ubiquitous markers, cell senescence has accessory characteristics, which mostly depend on senescence-inducing stimulus and/or cell type. Here, we review main markers and mechanisms involved in the induction of cell senescence with a focus on stress factor-dependent differences in signaling pathways activated in senescence.

K e y w o r d s: cell senescence, telomeres, DNA damage, irradiation, reactive oxygen species, oncogenes

Introduction

Features of cell senescence

Hayflick pioneered studies on cell aging in his experiments with primary human cell cultures. Cells were demonstrated to have a limited proliferative potential and to enter what is known as cell senescence after a certain number of divisions [1, 2]. The maximal number of divisions possible for somatic cells has been termed the Hayflick limit since that time. Olovnikov (1971) and Watson (1972) independently provided an elegant theoretical explanation for the phenomenon, describing this as the DNA end-replication problem [3, 4]. Far more recently, experimental findings to support the telomere molecular clock hypothesis were reported [5, 6]. Moreover, the causes of proliferative arrest and sub-

sequent cell senescence were found to include not only telomere shortening, but also a variety of stress factors, such as DNA damage, oxidative stress, oncogene activation, growth factor deficiency, and chemical exposure [7, 8]. Replicative senescence and stress-induced senescence (premature senescence) are commonly recognized as distinct phenomena. However, discrimination of replicative senescence and stress-induced senescence is mainly based on the nature of inducer, and many biochemical and morphological signs are common for the both types of cell senescence.

Accumulating experimental data allow considering cell senescence as one of the programs of cell stress response alongside with apoptosis, autophagy, necrosis, *etc*. As a process that globally affects cell fate, cell senescence has certain characteristics. Some of the characteristics are universal, while oth-

ers are accessory and vary with the nature of the stress-inducing factor and the cell line [9]. The main characteristics of cell senescence are the following.

(1) Changes in cell morphology. Cells enlarge and acquire flattened morphology. The size of cell nucleus increases several-fold; the number of nuclei may also increase in the cell. The Golgi system becomes more prominent, and extensive vacuolization of the cytoplasm is sometimes seen [10, 11].

(2) Higher activity of senescence-associated β-galactosidase (SA-β-Gal) at pH 6.0 [12]. Normally, β-galactosidase resides in lysosomes and works at acidic pH 4.0. SA-β-Gal activity detectable at a suboptimal pH 6.0 is currently thought to be due to an increase in lysosome content or β-galactosidase activity in senescent cells [13–15].

(3) Cyclin-dependent kinase inhibitors are upregulated to arrest cell proliferation. Two cyclin-dependent kinase inhibitors, p16^{INK4a} and p21$^{CIP1/WAF1}$, are the most typical of cell senescence [7, 16]. Ample experimental evidence indicate that p16^{INK4a} and p21$^{CIP1/WAF1}$ function independently of each other and are involved in two alternative signaling pathways [17] (Figure 1). Apart from the above proteins, other

Fig. 1. Simplified model of the stress-induced inhibition of the cell cycle progression (see the text for further details).

cyclin-dependent kinase inhibitors – p27^{KIP1}, p57^{KIP2}, and p15^{INK4b} – may contribute to the senescent phenotype, but their role was documented only in few particular cases of cell senescence [18–20].

Other cell senescence characteristics are accessory, helping rather to identify the senescence-inducing factor.

DNA damage signaling is one of the most common factors triggering the cell senescence [21]. Impaired DNA integrity activates repair systems (a DNA damage response, DDR), and repair proteins are recruited to the sites of DNA damage. Many repair-associated proteins, such as γH2AX, 53BP1, MDC1, NBS1, MRE11, and RAD17, concentrate in the so-called repair foci, which are detectable by cell immunostaining with corresponding antibodies [22, 23]. Persistent DDR can trigger cell senescence [21].

Condensed chromatin regions known as the senescence-associated heterochromatin foci (SAHF) form in the nuclei of senescent cells [24–26]. Cytologically, heterochromatin regions are detectable with the DAPI DNA intercalating dye. SAHF formation is accompanied by a decrease of nuclease sensitivity [24] and an accumulation of protein markers of transcriptionally inactive chromatin: histone H3 trimethylated at Lys9 (H3K9me3), heterochromatin protein 1γ (HP1γ), histone macroH2A, *etc.* [24–26]. Lamina-associated domains (LAD) detached from the lamina in senescent cells were recently shown to provide a structural basis of SAHF [27]. Oncogene overexpression and certain genotoxic agents are known to be the major inducers of cell senescence associated with SAHF formation [24, 28]. It should be noted that SAHF formation occurs only in certain cell lines and depends on the nature of the cell senescence-inducing agent [28]. Cell senescence accompanied by SAHF formation proceeds mostly via the p16^{INK4a}-dependent pathway [28].

Senescent cells retain high metabolic activity in spite of their proliferative arrest. Among other features, a specific senescence-associated secretory phenotype (SASP) is indicative of this activity [29]. Secretion of bioactive molecules, such as cytokines, is thought to provide for paracrine cell-to-cell communication and to trigger the inflammatory response
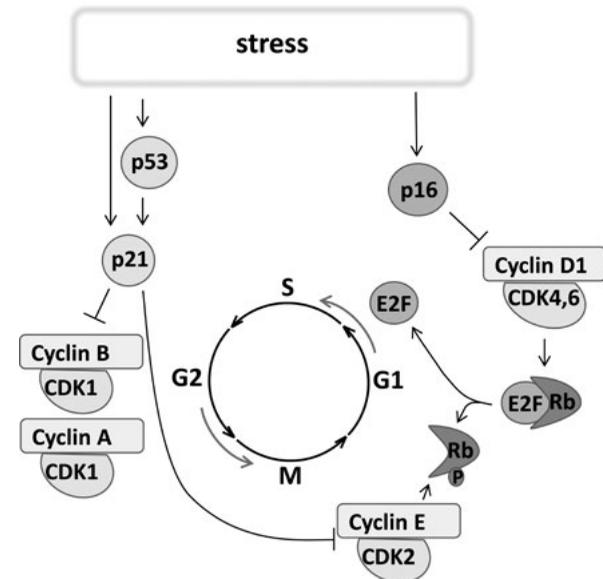
to eliminate cells with signs of senescence from the tissues [30]. The SASP is characterized by a slow development and takes several days to become detectable after the cell senescence program is triggered [31]. SASP activation involves the MAPK, mTOR, and DDR signaling pathways [32–34].

A comparison of microRNA expression between normal cells and cells with signs of senescence revealed several tens of senescence-associated microRNAs (SA-miRNAs), which are potentially involved in regulating development of the senescent phenotype [35, 36]. However, results from independent experiments lack correlation. Changes in expression were reliably reproduced for only four SA-miRNAs: miR-146a, -34a, -29, and -15a [37–46]. It is known that miR-146a inhibits SASP induction [44, 45]; that miR-34a overexpression is regulated by p53 [40, 47] and inhibits E2F signaling [39]; that miR-15a overexpression exerts a similar effect [48]; and that miR-29 downregulates the B-Myb transcription factor, which is necessary for the normal cell cycle progression [43]. The long noncoding RNA PANDA, which was identified recently, also belongs to noncoding RNAs involved in regulating cell senescence [49]. In complex with Polycomb group proteins, PANDA inhibits the NF-YA transcription factor to suppress cell senescence [49].

It should be noted that other events additionally accompany the large-scale metabolic reorganization in senescent cells. The extracellular matrix proteome changes [50, 51]; expression of vimentin, fibronectin [52, 53], and collagenase [54, 55] increases in some cases; the structure of the nuclear lamina is distorted [56, 57]; nuclear architecture undergoes substantial rearrangements [58, 59], retrotransposon transcription increases [60, 61], and the total epigenetic status of chromatin is altered [62].

The above changes arise from activation of the cell senescence program and develop in accord with the nature of the inducing stress factor and the cell line. A broad variety of optional (facultative) characters of cell senescence suggests a variety of signaling pathways involved in developing and maintaining the senescent phenotype. The mechanisms that po-

tentially mediate the induction and development of cell senescence are summarized below.

Causes of cell senescence

After Hayflick and Moorhead's experiments [1], two hypotheses were suggested to explain why normal cells stop proliferating [63]. One postulated that internal mechanisms determine a finite number of cell divisions. The other hypothesis suggested that lesions caused by physiological stresses accumulate in cultured cells to arrest their division, thus questioning the existence of the Hayflick limit [64]. Both of the hypotheses found support more recently as endogenous and exogenous factors were discovered to trigger the cell senescence.

Telomeric loop unwinding

Telomere shortening was the first to be noted as an internal trigger of replicative senescence [5]. In 1984, Greider and Blackburn worked with the ciliate *Tetrahymena thermophila* and identified telomerase as an enzyme that extends the 3' DNA end (G-strand) [65]. Telomerase produces a relatively long 3' single-stranded overhang, which is used as a template to synthesize a complementary DNA strand [65]. The total length of telomeric chromosome regions is thus increased. More recent studies showed that telomerase is absent from human somatic cells, while its activity is detectable in immortalized cells and the majority of cancer cells [66, 67]. These findings supported the telomeric molecular clock concept.

The telomere length was measured in individual cells and dividing cell populations and proved to vary greatly [68–70]. It was assumed accordingly that a synchronous shortening of all chromosomes is not necessary, while an impaired integrity of individual telomeres is sufficient for the induction of cell senescence [68, 71, 72]. Furthermore, it was shown that the mean 3'-overhang length of individual chromosomes, rather than the total telomere length [72, 73], and specific proteins present in telomeric regions [74] are important for triggering cell senescence.

Using electron microscopy Griffith *et al*. observed that telomeres are organized in the so-called t-loops

[75]. The t-loop formation depends on the presence of a 50- to 200-nt 3' single-stranded overhang, which hybridizes with an upstream double-stranded repeat to displace one of the strands [75]. A shortening of the 3' single-stranded overhang may cause a t-loop unwinding and trigger cell senescence [73]. An important role in organizing the t-loop is played by shelterin complex proteins, which protect the telomeres from unwarranted effects of repair systems and regulate telomerase activity [76–78]. The mammalian shelterin complex includes six proteins: TRF1, TRF2, RAP1, TIN2, POT1, and TPP1 [79]. Structural alterations of the shelterin complex trigger cell senescence. For instance, a mutant TRF2 that forms a heterodimer with the native TRF2 to block its binding to DNA induces a senescent phenotype when expressed in human cells [74, 78].

Thus, telomere loop unwinding is a more common phenomenon that triggers the cell senescence program. Its potential causes include (i) a total telomere length shortening, (ii) a shortening of the 3' single-stranded telomeric overhang, or (iii) alterations in the composition or structure of the shelterin complex. T-loop unwinding allows the chromosome end to be recognized as a double-stranded DNA break (DSB) and activates the DDR. There is strong evidence that the DDR signaling pathway triggers cell senescence when the telomere integrity is impaired [80, 81]. The model is supported by numerous findings of repair proteins, such as γH2AX and 53BP1, on telomeric repeats in senescent cells [82, 83]. Moreover, inactivation of DDR factors prevents cell senescence induced by telomere shortening [80, 84, 85].

Thus, replicative senescence is induced as a result of impaired telomere integrity and DDR activation. The p53 protein acts as one of the DDR effectors [86, 87] and is involved in regulating p21[CIP1/WAF1] expression [88, 89]. These observations agree with the data that the p21[CIP1/WAF1] signaling cascade plays a major role in cell senescence due to telomere dysfunction, while a role of p16[INK4a] is questionable for both humans and mice [74, 80, 85]. Of note, p16[INK4a] and p21[CIP1/WAF1] are sometimes coexpressed in replicative senescence, although different functions are ascribed

to them. It is thought that p21[CIP1/WAF1] and p53 play an important role in triggering cell senescence, while p16[INK4a] is necessary for its maintenance [90, 91].

DNA damage-induced cell senescence

DNA damage that does not affect the telomere structure also can trigger cell senescence [21]. Both exogenous and endogenous factors are sources of DNA lesions. The former include ultraviolet light (UV), ionizing radiation (IR), hyperthermia, reactive oxygen species (ROS), and genotoxic chemicals; and the latter, endogenous ROS and reactive nitrogen species, alkylating agents, spontaneous hydrolysis and deamination of nucleotides, replication and transcription errors, oncogene expression, and activation of cell nucleases [92, 93].

Proliferation arrest and a senescent phenotype are observed in cells exposed to IR, [94, 95], UV [96, 97], genotoxic agents [54, 98], or ROS [99, 100] or result from activated oncogene expression [101, 102].

IR-induced cell senescence

IR is a source of various DNA lesions, such as modified bases, apurinic/apyrimidinic (AP) sites, and single- (SSB) and double-stranded DNA breaks [103]. IR-induced DNA lesions were initially thought to cause apoptosis [104]. More recently, IR was found to suppress cell proliferation by triggering cell senescence. Thus cell senescence is induced in cultured normal human fibroblasts at 0.1–6 Gy [105], human umbilical vein endothelial cells at 4.0 Gy [106], mouse marrow cells at 4 Gy [107], mouse hematopoietic cells at 6.5 Gy [108] and human pulp stem cells at 20 Gy [109]. A senescence-like phenotype is similarly induced upon IR exposure (6.0–10 Gy) in cancer cells, including MCF7 breast [110, 111], human non-small cell lung [112], and PC-3 human prostate [113] cancer cells.

IR-induced DNA lesions activate ATM, ATR, DNA-PK and cause the formation of repair foci containing 53BP1 and γH2AX [114]. The majority of DNA lesions are repaired within one day, but γH2AX and 53BP1 repair foci may persist for up to several weeks [115]. The persistent DDR foci may trigger cell

senescence in case of IR [116]. IR-induced cell senescence proceeds via p53-dependent or p53-independent pathways. Phosphorylated p53 and the cyclin-dependent kinase inhibitor p21$^{CIP1/WAF1}$ accumulate in cells as a result of IR-induced senescence, as was observed in many studies [112, 116]. Phosphorylation of p53 in IR-exposed cells involves ATM and, possibly, ATR [86]. An ATM-independent pathway mediates IR-induced senescence in cells with inactivating mutations of the ATM gene and hTERT expression [117]. Changes in expression of p53, p21$^{CIP1/WAF1}$, and p16^{INK4a} are possibly related to activation of the MAPK signaling pathway [117]. The other pathway mediating senescence in IR-exposed cells depends on expression of the cyclin-dependent kinase inhibitor p16^{INK4a} and is p53 independent [118]. Coexpression of p21$^{CIP1/WAF1}$ and p16^{INK4a} is sometimes observed in cells after IR exposure, indicating that the two signaling cascades act together to mediate IR-induced senescence [94, 107, 109, 112].

It should be noted that ROS production may be involved in IR-induced cell senescence [119, 120]. Cells exposed to low-dose radiation affect the adjacent normal cells to activate the DDR and ROS production [121]. This IR effect is known as non-targeted bystander effect. DNA damage signals arise in the adjacent cells as a result of SASP induction and ROS generation by cells wherein IR triggered the senescence program [121, 122].

UV-induced cell senescence

UV acts as a potent genotoxic agent [123]. Photochemical reactions and severe UV-induced oxidative stress alter the nucleotide structure in DNA [124]. These lesions are repaired by nucleotide and base excision repair systems [125, 126] that introduce breaks in DNA strands in the course of their function. In addition, AP sites, SSBs, and DSBs arise in DNA upon exposure to UV [127, 128]. These lesions result from DNA replication fork collapse [129], inefficient or incorrect excision repair [130, 131], or the ROS effect [132]. UV-induced DNA lesions lead to the formation of DDR foci containing γH2AX, NBS1, Rad51, and XPA [133, 134].

High-dose UV irradiation usually induces apoptosis [135, 136], while low doses cause proliferative arrest with signs of cell senescence [137, 138]. By analogy with IR, DNA damage signals and oxidative stress can be assumed to trigger senescence in UV-exposed cells [138, 139]. Several signaling pathways are potentially involved in UV-induced cell senescence. One is the p53–p21$^{CIP1/WAF1}$-dependent pathway [140]. A role of the p16^{INK4a}-dependent pathway in UV-induced senescence cannot also be excluded [141]. A rapid increase in p16^{INK4a} expression and proliferative arrest are observed in normal and cancer cell cultures exposed to UV [142, 143]. Moreover, p16^{INK4a} overexpression in the cell substantially alleviates the cytotoxic effect of UV [144]. Signaling cascades from activated cell surface receptors may play a role in UV-induced cell senescence. For instance, IGF-1R proved to be necessary for triggering UV-induced senescence in human keratinocytes [97]. IGF-1R presumably activates the p38 MAPK signaling pathway to play a role in cell senescence [97].

ROS and cell senescence

ROS were found to play an important role in triggering and maintaining cell senescence [145]. Antioxidants abolish or suppress the development of cell senescence [146-148]. Moreover, organismal aging proved to directly correlate with an accumulation of oxidized proteins [149] and oxidized nucleotides [150] and an increase in DNA lesions [151]. NADPH oxidases and 5-lipoxygenase (5-LOX) are the main endogenous sources of ROS, and their activities can change in cell senescence [152–154].

ROS are capable of directly triggering cell senescence. ROS induction with hydrogen peroxide (H2O2) [99, 155–157] or tert-butylhydroperoxide (t-BHP) [158, 159] was observed to cause cell senescence. ROS induction is necessary for senescence due to interferon-β treatment [160]. The ROS content increases in replicative senescence and premature senescence triggered by IR, UV, or oncogene overexpression [120, 139, 161, 162]. Recent data support the idea that ROS not only induce cell senescence, but they are also necessary for making the

replicative arrest irreversible via positive feedback between ROS production and the DDR [147, 163, 164]. ROS were also demonstrated to play a role in accelerating replicative senescence [165].

The mechanism of triggering cell senescence by ROS is largely unclear. ROS affect a broad range of targets, including proteins, lipids, and nucleic acids [166]. ROS-mediated cell senescence is often associated with DDR activation as a result of DNA damage [147, 164]. Acting directly, ROS affect not only the DNA integrity, but also the functions of important transcription factors (NF-kB, AP-1, Nrf2, HIF) [167–169] and the signaling pathways (MAPK and PI3K/Akt) that regulate cell viability [170, 171].

The role of p53 and p21$^{CIP1/WAF1}$ in cell senescence associated with an increase in ROS was demonstrated in many experiments [155, 156, 158]. A knockdown of p53 and p21$^{CIP1/WAF1}$ substantially decreases the ROS production in replicative and non-replicative cell senescence [163]. There is evidence that cell senescence is maintained via a feedback loop involving an increase in ROS, generation of DNA lesions, and p21$^{CIP1/WAF1}$ expression in aging cells [163] (Figure 2). Moreover, p21$^{CIP1/WAF1}$ can contribute to the senescent phenotype in a p53-independent manner, by facilitating ROS production [100, 172]. Takahashi *et al*. showed that the cyclin-dependent
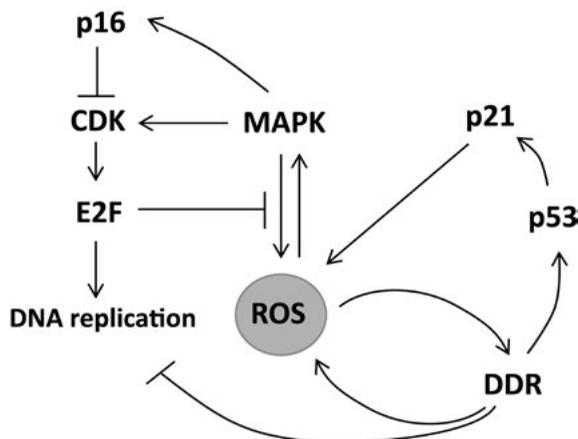

Fig. 2. Production of ROS may be enhanced by the functioning of a positive feedback loop between the MAPK and DDR signaling pathways and the action of the ROS (see the text for further details).

kinase inhibitor p16^{INK4a} is associated with ROS production through activation of the MAPK signaling pathway in human fibroblasts [173] (Figure 2).

Hypoxia-induced cell senescence

Given that ROS induce cell senescence, an opposite effect might be expected for hypoxia. In fact, there is ample evidence that hypoxia generally suppresses cell senescence [174, 175]. Hypoxia exerts an effect similar to that of the mTOR kinase inhibitor rapamycin, preventing the conversion of reversible proliferative arrest to p21$^{CIP1/WAF1}$-dependent senescence in both cancer and normal cells [176, 177]. Still, hypoxia was demonstrated to induce cell senescence *in vitro* [178–180] and *in vivo* [181].

Welford and Blagosklonny reviewed the roles of signaling pathways in activating or suppressing hypoxia-induced cell senescence [182, 183]. However, the problem is yet far from fully understood. Experiments with RNA interference showed that p53, p21$^{CIP1/WAF1}$, and p16^{INK4a} are not essential for triggering and maintaining of hypoxia-induced cell senescence [178, 180]. The antiapoptotic factor Bcl-2 was presumably implicated in triggering premature hypoxia-induced cell senescence [180].

Oncogene-induced cell senescence

The human genome has two groups of genes that differently influence the transformation of normal cells into cancer cells: oncogenes and tumor suppressor genes. A third group includes proto-oncogenes, which become oncogenes when affected by mutations. Mutations alter either the enzyme functions or the expression level of the affected gene. The protein products of many proto-oncogenes regulate the cell cycle progression, signal transduction, and cell differentiation. For example, the RAS, STAT5A, E2F1, WNT, EGFR, MYC, cyclin D1, cyclin E1, ERK, *etc.* are proto-oncogenes [184].

In 1997, Serrano *et al*. were the first to report experimental evidence that implicates oncogenes in triggering cell senescence [101]. Expression of the RAS^{V12} oncogene was shown to induce cell senescence in human and mouse primary fibroblasts.

Since that time, the list of potential oncogenes capable of inducing cell senescence has been substantially extended, and the relevant senescence type was termed oncogene-induced senescence (OIS) [185]. Of note, the PTEN, NF1, and VHL tumor suppressor genes were additionally identified as genes whose mutations lead to cell senescence [186–188].

Two basically different models were proposed to explain the mechanisms of OIS [189]. One implies DDR activation as a main event in triggering OIS [190]. An important argument in favor of this model is provided by the experimental finding that inhibition of DDR (ATM, ATR, p53, CHK1, CHK2) gene expression completely or partly suppresses OIS [191-193]. Oncogene-induced DDR is thought to result from ROS production in the cell [162, 194]. A substantial increase in ROS production upon oncogene overexpression was demonstrated with the example of RAS and MYC [162, 194–198]. Inhibition of ROS production was shown to prevent RAS-induced cell senescence [162, 194]. Replicative stress due to a change in the velocity of DNA replication forks is another possible mechanism of oncogene-induced DDR [191, 198–200]. In this case, cell senescence may be caused by depletion of the nucleotide pool [201], an accumulation of oxidized nucleotides [197], replication fork reversal [198, 200], or DNA re-replication [191]. Activation of DDR components plays a main role in triggering cell senescence in this case, while the presence of DNA breaks is not necessary [190].

Another model assumes that DDR activation is not necessary for OIS induction and that oncogene expression triggers the biochemical cascades that activate transcription of the CDKN2A genomic locus, which codes for $p16^{INK4a}$ and ARF ($p14^{ARF}$ in humans and $p19^{ARF}$ in mice) [202, 203]. Activation of their genes leads to cell senescence. The model is supported by the fact that ectopic expression of $p16^{INK4a}$ and $p21^{CIP1/WAF1}$ is sufficient for the development of a senescent phenotype [204–206]. Moreover, oncogenes do not always trigger the DDR and the formation of repair foci [207, 208]. A DDR-independent OIS implies the involvement of two signaling cascades,

$ARF–p53–p21^{CIP1/WAF1}$ [102, 186, 209] and $p16^{INK4a}$–pRb [101, 205]. ARF was observed to induce proliferative arrest via a p53-dependent pathway, by inhibiting p53 degradation [210]. This role is possibly not the only one ARF plays in triggering OIS [211]. There is also an opinion that ARF acts as an accessory, rather than driving, factor in OIS [101, 212].

Other signaling cascades may be involved in OIS as well. For instance, many oncogenes – RAS, RAF, ERK, and MEK – code for components of the MAPK signaling pathway [213]. Overexpression of MEK is alone sufficient to appreciably increase the p53 and $p16^{INK4a}$ levels and to induce cell senescence [214]. The findings suggest complementary action in OIS for the MAPK, $p53–p21^{CIP1/WAF1}$, and $p16^{INK4a}$–pRb signaling pathways [187, 205, 213]

It is important to note that activation of a particular signaling pathway depends not only on the oncogene, but also on the cell line. For instance, the $BRAF^{V600E}$ oncogene activates $p16^{INK4a}$- and PI3K-dependent pathways in human melanocytes, while a $p16^{INK4a}$-independent pathway mediates $BRAF^{V600E}$-induced senescence in mouse cells [215–217]. Moreover, OIS is not induced at all in some cells [218].

Conclusions

Here, we review main markers and mechanisms involved in the induction of cell senescence. It is obvious that the senescent cells share several most crucial features, such as lack of DNA synthesis, increased SA-β-gal activity and upregulation of cyclin-dependent kinase inhibitors. Most of these universal senescence markers are indicative not only for cell senescence but for other types of growth arrest as well. At the same time particular senescent cell may have a number of accessory unique senescence-associated characteristics, which mostly depend on senescence-inducing stimulus and/or cell type. It might be useful to develop clear system of cell senescence phenotype classification.

Acknowledgements

REFERENCES

1. *Hayflick L, Moorhead PS.* The serial cultivation of human diploid cell strains. *Exp Cell Res.* 1961;**25**:585–621.

2. *Hayflick L.* The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res.* 1965;**37**:614–36.

3. *Olovnikov AM.* [Principle of marginotomy in template synthesis of polynucleotides]. *Dokl Akad Nauk SSSR.* 1971;**201**(6):1496–9.

4. *Watson JD.* Origin of concatemeric T7 DNA. *Nat New Biol.* 1972;**239**(94):197–201.

5. *Harley CB, Futcher AB, Greider CW.* Telomeres shorten during ageing of human fibroblasts. *Nature.* 1990;**345**(6274):458–60.

6. *Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, et al.* Extension of life-span by introduction of telomerase into normal human cells. *Science.* 1998;**279**(5349):349–52.

7. *Ben-Porath I, Weinberg RA.* The signals and pathways activating cellular senescence. *Int J Biochem Cell Biol.* 2005;**37**(5):961–76.

8. *Campisi J.* Aging, cellular senescence, and cancer. *Annu Rev Physiol.* 2013;**75**:685–705.

9. *Kuilman T, Michaloglou C, Mooi WJ, Peeper DS.* The essence of senescence. *Genes Dev.* 2010;**24**(22):2463–79.

10. *Robbins E, Levine EM, Eagle H.* Morphologic changes accompanying senescence of cultured human diploid cells. *J Exp Med.* 1970;**131**(6):1211–22.

11. *Greenberg SB, Grove GL, Cristofalo VJ.* Cell size in aging monolayer cultures. *In Vitro.* 1977;**13**(5):297–300.

12. *Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, et al.* A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proc Natl Acad Sci U S A.* 1995;**92**(20):9363–7.

13. *Kurz DJ, Decary S, Hong Y, Erusalimsky JD.* Senescence-associated (beta)-galactosidase reflects an increase in lysosomal mass during replicative ageing of human endothelial cells. *J Cell Sci.* 2000;**113** (Pt 20):3613–22.

14. *Lee BY, Han JA, Im JS, Morrone A, Johung K, Goodwin EC, Kleijer WJ, DiMaio D, Hwang ES.* Senescence-associated beta-galactosidase is lysosomal beta-galactosidase. *Aging Cell.* 2006;**5**(2):187–95.

15. *Michaloglou C, Soengas MS, Mooi WJ, Peeper DS.* Comment on "Absence of senescence-associated beta-galactosidase activity in human melanocytic nevi in vivo". *J Invest Dermatol.* 2008;**128**(6):1582–3; author reply 1583–4.

16. *Campisi J, d'Adda di Fagagna F.* Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol.* 2007;**8**(9):729–40.

17. *Fang L, Igarashi M, Leung J, Sugrue MM, Lee SW, Aaronson SA.* p21Waf1/Cip1/Sdi1 induces permanent growth arrest with markers of replicative senescence in human tumor cells lacking functional p53. *Oncogene.* 1999;**18**(18):2789–97.

18. *Malumbres M, Pérez De Castro I, Hernández MI, Jiménez M, Corral T, Pellicer A.* Cellular response to oncogenic ras involves induction of the Cdk4 and Cdk6 inhibitor p15(INK4b). *Mol Cell Biol.* 2000;**20**(8):2915–25.

19. *Tsugu A, Sakai K, Dirks PB, Jung S, Weksberg R, Fei YL, et al.* Expression of p57(KIP2) potently blocks the growth of human astrocytomas and induces cell senescence. *Am J Pathol.* 2000;**157**(3):919–32.

20. *Munro J, Steeghs K, Morrison V, Ireland H, Parkinson EK.* Human fibroblast replicative senescence can occur in the absence of extensive cell division and short telomeres. *Oncogene.* 2001;**20**(27):3541–52.

21. *d'Adda di Fagagna F.* Living on a break: cellular senescence as a DNA-damage response. *Nat Rev Cancer.* 2008;**8**(7):512–22.

22. *Lukas C, Savic V, Bekker-Jensen S, Doil C, Neumann B, Pedersen RS, et al.* 53BP1 nuclear bodies form around DNA lesions generated by mitotic transmission of chromosomes under replication stress. *Nat Cell Biol.* 2011;**13**(3):243–53.

23. *Wang Q, Goldstein M, Alexander P, Wakeman TP, Sun T, Feng J, Lou Z, Kastan MB, Wang XF.* Rad17 recruits the MRE11-RAD50-NBS1 complex to regulate the cellular response to DNA double-strand breaks. *EMBO J.* 2014;**33**(8):862–77.

24. *Narita M, Nũnez S, Heard E, Narita M, Lin AW, Hearn SA, Spector DL, Hannon GJ, Lowe SW.* Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. *Cell.* 2003;**113**(6):703–16.

25. *Narita M, Narita M, Krizhanovsky V, Nuñez S, Chicas A, Hearn SA, Myers MP, Lowe SW.* A novel role for high-mobility group a proteins in cellular senescence and heterochromatin formation. *Cell.* 2006;**126**(3):503–14.

26. *Zhang R, Poustovoitov MV, Ye X, Santos HA, Chen W, Daganzo SM, et al.* Formation of MacroH2A-containing senescence-associated heterochromatin foci and senescence driven by ASF1a and HIRA. *Dev Cell.* 2005;**8**(1):19–30.

27. *Chandra T, Ewels PA, Schoenfelder S, Furlan-Magaril M, Wingett SW, Kirschner K, et al.* Global reorganization of the nuclear landscape in senescent cells. *Cell Rep.* 2015;**10**(4):471–83.

28. *Kosar M, Bartkova J, Hubackova S, Hodny Z, Lukas J, Bartek J.* Senescence-associated heterochromatin foci are dispensable for cellular senescence, occur in a cell type- and insult-dependent manner and follow expression of p16(ink4a). *Cell Cycle.* 2011;**10**(3):457–68.

29. *Coppé JP, Desprez PY, Krtolica A, Campisi J.* The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol.* 2010;**5**:99–118.

30. *Pérez-Mancera PA, Young AR, Narita M.* Inside and out: the activities of senescence in cancer. *Nat Rev Cancer.* 2014;**14**(8):547–58.

31. *Rodier F, Coppé JP, Patil CK, Hoeijmakers WA, Muñoz DP, Raza SR, et al.* Persistent DNA damage signalling triggers

senescence-associated inflammatory cytokine secretion. *Nat Cell Biol.* 2009;**11**(8):973–9.

32. *Freund A, Patil CK, Campisi J.* p38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. *EMBO J.* 2011;**30**(8):1536–48.

33. *Laberge RM, Sun Y, Orjalo AV, Patil CK, Freund A, Zhou L, et al.* MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. *Nat Cell Biol.* 2015;**17**(8):1049–61.

34. *Acosta JC, O'Loghlen A, Banito A, Guijarro MV, Augert A, Raguz S, et al.* Chemokine signaling via the CXCR2 receptor reinforces senescence. *Cell.* 2008;**133**(6):1006–18.

35. *Lafferty-Whyte K, Cairney CJ, Jamieson NB, Oien KA, Keith WN.* Pathway analysis of senescence-associated miRNA targets reveals common processes to different senescence induction mechanisms. *Biochim Biophys Acta.* 2009;**1792**(4):341–52.

36. *Smith-Vikos T, Slack FJ.* MicroRNAs and their roles in aging. *J Cell Sci.* 2012;**125**(Pt 1):7–17.

37. *Zhao T, Li J, Chen AF.* MicroRNA-34a induces endothelial progenitor cell senescence and impedes its angiogenesis via suppressing silent information regulator 1. *Am J Physiol Endocrinol Metab.* 2010;**299**(1):E110–6.

38. *Li N, Muthusamy S, Liang R, Sarojini H, Wang E.* Increased expression of miR-34a and miR-93 in rat liver during aging, and their impact on the expression of Mgst1 and Sirt1. *Mech Ageing Dev.* 2011;**132**(3):75–85.

39. *Tazawa H, Tsuchiya N, Izumiya M, Nakagama H.* Tumor-suppressive miR-34a induces senescence-like growth arrest through modulation of the E2F pathway in human colon cancer cells. *Proc Natl Acad Sci U S A.* 2007;**104**(39):15472–7.

40. *Kumamoto K, Spillare EA, Fujita K, Horikawa I, Yamashita T, Appella E, et al.* Nutlin-3a activates p53 to both down-regulate inhibitor of growth 2 and up-regulate mir-34a, mir-34b, and mir-34c expression, and induce senescence. *Cancer Res.* 2008;**68**(9):3193–203.

41. *Ugalde AP, Ramsay AJ, de la Rosa J, Varela I, Mariño G, Cadiñanos J, Lu J, Freije JM, López-Otín C.* Aging and chronic DNA damage response activate a regulatory pathway involving miR-29 and p53. *EMBO J.* 2011;**30**(11):2219–32.

42. *Wagner W, Horn P, Castoldi M, Diehlmann A, Bork S, Saffrich R, Benes V, Blake J, Pfister S, Eckstein V, Ho AD.* Replicative senescence of mesenchymal stem cells: a continuous and organized process. *PLoS One.* 2008;**3**(5):e2213.

43. *Martinez I, Cazalla D, Almstead LL, Steitz JA, DiMaio D.* miR-29 and miR-30 regulate B-Myb expression during cellular senescence. *Proc Natl Acad Sci U S A.* 2011;**108**(2):522–7.

44. *Bhaumik D, Scott GK, Schokrpur S, Patil CK, Orjalo AV, Rodier F, Lithgow GJ, Campisi J.* MicroRNAs miR-146a/b negatively modulate the senescence-associated inflammatory mediators IL-6 and IL-8. *Aging (Albany NY).* 2009;**1**(4):402–11.

45. *Li G, Luna C, Qiu J, Epstein DL, Gonzalez P.* Modulation of inflammatory markers by miR-146a during replicative senescence in trabecular meshwork cells. *Invest Ophthalmol Vis Sci.* 2010;**51**(6):2976–85.

46. *Bonifacio LN, Jarstfer MB.* MiRNA profile associated with replicative senescence, extended cell culture, and ectopic telomerase expression in human foreskin fibroblasts. *PLoS One.* 2010;**5**(9). pii: e12519.

47. *He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, et al.* A microRNA component of the p53 tumour suppressor network. *Nature.* 2007;**447**(7148):1130–4.

48. *Ofir M, Hacohen D, Ginsberg D.* MiR-15 and miR-16 are direct transcriptional targets of E2F1 that limit E2F-induced proliferation by targeting cyclin E. *Mol Cancer Res.* 2011;**9**(4):440–7.

49. *Puvvula PK, Desetty RD, Pineau P, Marchio A, Moon A, Dejean A, Bischof O.* Long noncoding RNA PANDA and scaffold-attachment-factor SAFA control senescence entry and exit. *Nat Commun.* 2014;**5**:5323.

50. *Benanti JA, Williams DK, Robinson KL, Ozer HL, Galloway DA.* Induction of extracellular matrix-remodeling genes by the senescence-associated protein APA-1. *Mol Cell Biol.* 2002;**22**(21):7385–97.

51. *Yang KE, Kwon J, Rhim JH, Choi JS, Kim SI, Lee SH, Park J, Jang IS.* Differential expression of extracellular matrix proteins in senescent and young human fibroblasts: a comparative proteomics and microarray study. *Mol Cells.* 2011;**32**(1):99–106.

52. *Kaneko S, Satoh Y, Ikemura K, Konishi T, Ohji T, Karasaki Y, Higashi K, Gotoh S.* Alterations of expression of the cytoskeleton after immortalization of human fibroblasts. *Cell Struct Funct.* 1995;**20**(1):107–15.

53. *Maya-Mendoza A, Merchut-Maya JM, Bartkova J, Bartek J, Streuli CH, Jackson DA.* Immortalised breast epithelia survive prolonged DNA replication stress and return to cycle from a senescent-like state. *Cell Death Dis.* 2014;**5**:e1351.

54. *Robles SJ, Adami GR.* Agents that cause DNA double strand breaks lead to p16INK4a enrichment and the premature senescence of normal fibroblasts. *Oncogene.* 1998;**16**(9):1113–23.

55. *Palaniyappan A.* Cyclophosphamide induces premature senescence in normal human fibroblasts by activating MAP kinases. *Biogerontology.* 2009;**10**(6):677–82.

56. *Shimi T, Butin-Israeli V, Adam SA, Hamanaka RB, Goldman AE, Lucas CA, et al.* The role of nuclear lamin B1 in cell proliferation and senescence. *Genes Dev.* 2011;**25**(24):2579–93.

57. *Freund A, Laberge RM, Demaria M, Campisi J.* Lamin B1 loss is a senescence-associated biomarker. *Mol Biol Cell.* 2012;**23**(11):2066–75.

58. *Bridger JM, Boyle S, Kill IR, Bickmore WA.* Re-modelling of nuclear architecture in quiescent and senescent human fibroblasts. *Curr Biol.* 2000;**10**(3):149–52.

59. *Kar B, Liu B, Zhou Z, Lam YW.* Quantitative nucleolar proteomics reveals nuclear re-organization during stress- induced senescence in mouse fibroblast. *BMC Cell Biol.* 2011;**12**:33.

60. *Belancio VP, Roy-Engel AM, Pochampally RR, Deininger P.* Somatic expression of LINE-1 elements in human tissues. *Nucleic Acids Res.* 2010;**38**(12):3909–22.

61. *De Cecco M, Criscione SW, Peterson AL, Neretti N, Sedivy JM, Kreiling JA.* Transposable elements become active and mobile in the genomes of aging mammalian somatic tissues. *Aging (Albany NY).* 2013;**5**(12):867–83.

62. *Koch CM, Wagner W.* Epigenetic biomarker to determine replicative senescence of cultured cells. *Methods Mol Biol.* 2013;**1048**:309–21.

63. *Shay JW, Wright WE.* Hayflick, his limit, and cellular ageing. *Nat Rev Mol Cell Biol.* 2000;**1**(1):72–6.

64. *Rubin H.* Telomerase and cellular lifespan: ending the debate? *Nat Biotechnol.* 1998;**16**(5):396–7.

65. *Greider CW, Blackburn EH.* Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. *Cell.* 1985;**43**(2 Pt 1):405–13.

66. *Morin GB.* The human telomere terminal transferase enzyme is a ribonucleoprotein that synthesizes TTAGGG repeats. *Cell.* 1989;**59**(3):521–9.

67. *Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PL, Coviello GM, Wright WE, Weinrich SL, Shay JW.* Specific association of human telomerase activity with immortal cells and cancer. *Science.* 1994;**266**(5193):2011–5.

68. *Martens UM, Chavez EA, Poon SS, Schmoor C, Lansdorp PM.* Accumulation of short telomeres in human fibroblasts prior to replicative senescence. *Exp Cell Res.* 2000;**256**(1):291–9.

69. *Baird DM, Rowson J, Wynford-Thomas D, Kipling D.* Extensive allelic variation and ultrashort telomeres in senescent human cells. *Nat Genet.* 2003;**33**(2):203–7.

70. *Martin-Ruiz C, Saretzki G, Petrie J, Ladhoff J, Jeyapalan J, Wei W, Sedivy J, von Zglinicki T.* Stochastic variation in telomere shortening rate causes heterogeneity of human fibroblast replicative life span. *J Biol Chem.* 2004;**279**(17):17826–33.

71. *Zou Y, Sfeir A, Gryaznov SM, Shay JW, Wright WE.* Does a sentinel or a subset of short telomeres determine replicative senescence? *Mol Biol Cell.* 2004;**15**(8):3709–18.

72. *Chai W, Shay JW, Wright WE.* Human telomeres maintain their overhang length at senescence. *Mol Cell Biol.* 2005;**25**(6):2158–68.

73. *Stewart SA, Ben-Porath I, Carey VJ, O'Connor BF, Hahn WC, Weinberg RA.* Erosion of the telomeric single-strand overhang at replicative senescence. *Nat Genet.* 2003;**33**(4):492–6.

74. *Smogorzewska A, de Lange T.* Different telomere damage signaling pathways in human and mouse cells. *EMBO J.* 2002;**21**(16):4338–48.

75. *Griffith JD, Comeau L, Rosenfield S, Stansel RM, Bianchi A, Moss H, de Lange T.* Mammalian telomeres end in a large duplex loop. *Cell.* 1999;**97**(4):503–14.

76. *Celli GB, de Lange T.* DNA processing is not required for ATM-mediated telomere damage response after TRF2 deletion. *Nat Cell Biol.* 2005;**7**(7):712–8.

77. *Hockemeyer D, Sfeir AJ, Shay JW, Wright WE, de Lange T.* POT1 protects telomeres from a transient DNA damage response and determines how human chromosomes end. *EMBO J.* 2005;**24**(14):2667–78.

78. *van Steensel B, de Lange T.* Control of telomere length by the human telomeric protein TRF1. *Nature.* 1997;**385**(6618):740–3.

79. *de Lange T.* Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev.* 2005;**19**(18):2100–10.

80. *d'Adda di Fagagna F, Reaper PM, Clay-Farrace L, Fiegler H, Carr P, Von Zglinicki T, et al.* A DNA damage checkpoint response in telomere-initiated senescence. *Nature.* 2003;**426**(6963):194–8.

81. *Deng Y, Chan SS, Chang S.* Telomere dysfunction and tumour suppression: the senescence connection. *Nat Rev Cancer.* 2008;**8**(6):450–8.

82. *Peuscher MH, Jacobs JJ.* DNA-damage response and repair activities at uncapped telomeres depend on RNF8. *Nat Cell Biol.* 2011;**13**(9):1139–45.

83. *Fumagalli M, Rossiello F, Clerici M, Barozzi S, Cittaro D, Kaplunov JM, et al.* Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. *Nat Cell Biol.* 2012;**14**(4):355–65.

84. *Takai H, Smogorzewska A, de Lange T.* DNA damage foci at dysfunctional telomeres. *Curr Biol.* 2003;**13**(17):1549–56.

85. *Herbig U, Jobling WA, Chen BP, Chen DJ, Sedivy JM.* Telomere shortening triggers senescence of human cells through a pathway involving ATM, p53, and p21(CIP1), but not p16(INK4a). *Mol Cell.* 2004;**14**(4):501–13.

86. *Tibbetts RS, Brumbaugh KM, Williams JM, Sarkaria JN, Cliby WA, Shieh SY, Taya Y, Prives C, Abraham RT.* A role for ATR in the DNA damage-induced phosphorylation of p53. *Genes Dev.* 1999;**13**(2):152–7.

87. *Banin S, Moyal L, Shieh S, Taya Y, Anderson CW, Chessa L, et al.* Enhanced phosphorylation of p53 by ATM in response to DNA damage. *Science.* 1998;**281**(5383):1674–7.

88. *Barlev NA, Liu L, Chehab NH, Mansfield K, Harris KG, Halazonetis TD, Berger SL.* Acetylation of p53 activates transcription through recruitment of coactivators/histone acetyltransferases. *Mol Cell.* 2001;**8**(6):1243–54.

89. *Saramäki A, Banwell CM, Campbell MJ, Carlberg C.* Regulation of the human p21(waf1/cip1) gene promoter via multiple binding sites for p53 and the vitamin D3 receptor. *Nucleic Acids Res.* 2006;**34**(2):543–54.

90. *Alcorta DA, Xiong Y, Phelps D, Hannon G, Beach D, Barrett JC.* Involvement of the cyclin-dependent kinase inhibitor p16 (INK4a) in replicative senescence of normal human fibroblasts. *Proc Natl Acad Sci U S A.* 1996;**93**(24):13742–7.

91. *Stein GH, Drullinger LF, Soulard A, Dulić V.* Differential roles for cyclin-dependent kinase inhibitors p21 and p16 in the mechanisms of senescence and differentiation in human fibroblasts. *Mol Cell Biol.* 1999;**19**(3):2109–17.

92. *De Bont R, van Larebeke N.* Endogenous DNA damage in humans: a review of quantitative data. *Mutagenesis.* 2004;**19**(3):169–85.

93. *Ghosal G, Chen J.* DNA damage tolerance: a double-edged sword guarding the genome. *Transl Cancer Res.* 2013;**2**(3):107–129.

94. *Suzuki K, Mori I, Nakayama Y, Miyakoda M, Kodama S, Watanabe M.* Radiation-induced senescence-like growth arrest requires TP53 function but not telomere shortening. *Radiat Res.* 2001;**155**(1 Pt 2):248–253.

95. *Sabin RJ, Anderson RM.* Cellular Senescence – its role in cancer and the response to ionizing radiation. *Genome Integr.* 2011;**2**(1):7.

96. *Chaturvedi V, Qin JZ, Stennett L, Choubey D, Nickoloff BJ.* Resistance to UV-induced apoptosis in human keratinocytes during accelerated senescence is associated with functional inactivation of p53. *J Cell Physiol.* 2004;**198**(1):100–9.

97. *Lewis DA, Yi Q, Travers JB, Spandau DF.* UVB-induced senescence in human keratinocytes requires a functional insulin-like growth factor-1 receptor and p53. *Mol Biol Cell.* 2008;**19**(4):1346–53.

98. *Wang Y, Blandino G, Oren M, Givol D.* Induced p53 expression in lung cancer cell line promotes cell senescence and differentially modifies the cytotoxicity of anti-cancer drugs. *Oncogene.* 1998;**17**(15):1923–30.

99. *Chen Q, Ames BN.* Senescence-like growth arrest induced by hydrogen peroxide in human diploid fibroblast F65 cells. *Proc Natl Acad Sci U S A.* 1994;**91**(10):4130–4.

100. *Macip S, Igarashi M, Fang L, Chen A, Pan ZQ, Lee SW, Aaronson SA.* Inhibition of p21-mediated ROS accumulation can rescue p21-induced senescence. *EMBO J.* 2002;**21**(9):2180–8.

101. *Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW.* Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. *Cell.* 1997;**88**(5):593–602.

102. *Ferbeyre G, de Stanchina E, Lin AW, Querido E, McCurrach ME, Hannon GJ, Lowe SW.* Oncogenic ras and p53 cooperate to induce cellular senescence. *Mol Cell Biol.* 2002;**22**(10):3497–508.

103. *Lomax ME, Folkes LK, O'Neill P.* Biological consequences of radiation-induced DNA damage: relevance to radiotherapy. *Clin Oncol (R Coll Radiol).* 2013;**25**(10):578–85.

104. *Dewey WC, Ling CC, Meyn RE.* Radiation-induced apoptosis: relevance to radiotherapy. *Int J Radiat Oncol Biol Phys.* 1995;**33**(4):781–96.

105. *Di Leonardo A, Linke SP, Clarkin K, Wahl GM.* DNA damage triggers a prolonged p53-dependent G1 arrest and long-term induction of Cip1 in normal human fibroblasts. *Genes Dev.* 1994;**8**(21):2540–51.

106. *Kim KS, Kim JE, Choi KJ, Bae S, Kim DH.* Characterization of DNA damage-induced cellular senescence by ionizing radiation in endothelial cells. *Int J Radiat Biol.* 2014;**90**(1):71–80.

107. *Meng A, Wang Y, Van Zant G, Zhou D.* Ionizing radiation and busulfan induce premature senescence in murine bone marrow hematopoietic cells. *Cancer Res.* 2003;**63**(17):5414–9.

108. *Wang Y, Schulte BA, LaRue AC, Ogawa M, Zhou D.* Total body irradiation selectively induces murine hematopoietic stem cell senescence. *Blood.* 2006;**107**(1):358–66.

109. *Muthna D, Soukup T, Vavrova J, Mokry J, Cmielova J, Visek B, Jiroutova A, Havelek R, Suchanek J, Filip S, English D, Rezacova M.* Irradiation of adult human dental pulp stem cells provokes activation of p53, cell cycle arrest, and senescence but not apoptosis. *Stem Cells Dev.* 2010;**19**(12):1855–62.

110. *Jones KR, Elmore LW, Jackson-Cook C, Demasters G, Povirk LF, Holt SE, Gewirtz DA.* p53-Dependent accelerated senescence induced by ionizing radiation in breast tumour cells. *Int J Radiat Biol.* 2005;**81**(6):445–58.

111. *Kim BC, Han NK, Byun HO, Kim SS, Ahn EK, Chu IS, Leem SH, Lee CK, Lee JS.* Time-dependently expressed markers and the characterization for premature senescence induced by ionizing radiation in MCF7. *Oncol Rep.* 2010;**24**(2):395–403.

112. *Luo H, Yount C, Lang H, Yang A, Riemer EC, Lyons K, Vanek KN, Silvestri GA, Schulte BA, Wang GY.* Activation of p53 with Nutlin-3a radiosensitizes lung cancer cells via enhancing radiation-induced premature senescence. *Lung Cancer.* 2013;**81**(2):167–73.

113. *Barreto-Andrade JC, Efimova EV, Mauceri HJ, Beckett MA, Sutton HG, Darga TE, Vokes EE, Posner MC, Kron SJ, Weichselbaum RR.* Response of human prostate cancer cells and tumors to combining PARP inhibition with ionizing radiation. *Mol Cancer Ther.* 2011;**10**(7):1185–93.

114. *Kumar R, Horikoshi N, Singh M, Gupta A, Misra HS, Albuquerque K, et al* Chromatin modifications and the DNA damage response to ionizing radiation. Front Oncol. *2013;2:214.*

115. *Le ON, Rodier F, Fontaine F, Coppe JP, Campisi J, DeGregori J, et al.* Ionizing radiation-induced long-term expression of senescence markers in mice is independent of p53 and immune status. *Aging Cell.* 2010;**9**(3):398–409.

116. *Suzuki M, Suzuki K, Kodama S, Watanabe M.* Interstitial chromatin alteration causes persistent p53 activation involved in the radiation-induced senescence-like growth arrest. *Biochem Biophys Res Commun.* 2006;**340**(1):145–50.

117. *Naka K, Tachibana A, Ikeda K, Motoyama N.* Stress-induced premature senescence in hTERT-expressing ataxia telangiectasia fibroblasts. *J Biol Chem.* 2004;**279**(3):2030–7.

118. *Carbonneau CL, Despars G, Rojas-Sutterlin S, Fortin A, Le O, Hoang T, Beauséjour CM.* Ionizing radiation-induced expression of INK4a/ARF in murine bone marrow-derived stromal cell populations interferes with bone marrow homeostasis. *Blood.* 2012;**119**(3):717–26.

119. *Nelson G, Wordsworth J, Wang C, Jurk D, Lawless C, Martin-Ruiz C, von Zglinicki T.* A senescent cell bystander effect: senescence-induced senescence. *Aging Cell.* 2012;**11**(2):345–9.

120. *Hong EH, Lee SJ, Kim JS, Lee KH, Um HD, Kim JH, Kim SJ, Kim JI, Hwang SG.* Ionizing radiation induces cellular senescence of articular chondrocytes via negative regulation of SIRT1 by p38 kinase. *J Biol Chem.* 2010;**285**(2):1283–95.

121. *Dickey JS, Baird BJ, Redon CE, Sokolov MV, Sedelnikova OA, Bonner WM.* Intercellular communication of cellular stress monitored by gamma-H2AX induction. *Carcinogenesis.* 2009;**30**(10):1686–95.

122. *Azzam EI, de Toledo SM, Little JB.* Direct evidence for the participation of gap junction-mediated intercellular communication in the transmission of damage signals from alpha-particle irradiated to nonirradiated cells. *Proc Natl Acad Sci U S A.* 2001;**98**(2):473–8.

123. *Ravanat JL, Douki T, Cadet J.* Direct and indirect effects of UV radiation on DNA and its components. *J Photochem Photobiol B.* 2001;**63**(1–3):88–102.

124. *Sinha RP, Häder DP.* UV-induced DNA damage and repair: a review. *Photochem Photobiol Sci.* 2002;**1**(4):225–36.

125. *Sugasawa K, Okuda Y, Saijo M, Nishi R, Matsuda N, Chu G, et al.* UV-induced ubiquitylation of XPC protein mediated by UV-DDB-ubiquitin ligase complex. *Cell.* 2005;**121**(3):387–400.

126. *Scott AD, Waters R.* Inducible nucleotide excision repair (NER) of UV-induced cyclobutane pyrimidine dimers in the cell cycle of the budding yeast Saccharomyces cerevisiae: evidence that inducible NER is confined to the G1 phase of the mitotic cell cycle. *Mol Gen Genet.* 1997;**254**(1):43–53.

127. *Slieman TA, Nicholson WL.* Artificial and solar UV radiation induces strand breaks and cyclobutane pyrimidine dimers in Bacillus subtilis spore DNA. *Appl Environ Microbiol.* 2000;**66**(1):199–205.

128. *Baumstark-Khan C, Hentschel U, Nikandrova Y, Krug J, Horneck G.* Fluorometric analysis of DNA unwinding (FADU) as a method for detecting repair-induced DNA strand breaks in UV-irradiated mammalian cells. *Photochem Photobiol.* 2000;**72**(4):477–84.

129. *Batista LF, Kaina B, Meneghini R, Menck CF.* How DNA lesions are turned into powerful killing structures: insights from UV-induced apoptosis. *Mutat Res.* 2009;**681**(2–3):197–208.

130. *Limoli CL, Giedzinski E, Bonner WM, Cleaver JE.* UV-induced replication arrest in the xeroderma pigmentosum variant leads to DNA double-strand breaks, gamma -H2AX formation, and Mre11 relocalization. *Proc Natl Acad Sci U S A.* 2002;**99**(1):233–8.

131. *Vilenchik MM, Knudson AG.* Endogenous DNA double-strand breaks: production, fidelity of repair, and induction of cancer. *Proc Natl Acad Sci U S A.* 2003;**100**(22):12871–6.

132. *Greinert R, Volkmer B, Henning S, Breitbart EW, Greulich KO, Cardoso MC, Rapp A.* UVA-induced DNA double-strand breaks result from the repair of clustered oxidative DNA damages. *Nucleic Acids Res.* 2012;**40**(20):10263–73.

133. *Staszewski O, Nikolova T, Kaina B.* Kinetics of gamma-H2AX focus formation upon treatment of cells with UV light and alkylating agents. *Environ Mol Mutagen.* 2008;**49**(9):734–40.

134. *Wu X, Shell SM, Liu Y, Zou Y.* ATR-dependent checkpoint modulates XPA nuclear import in response to UV irradiation. *Oncogene.* 2007;**26**(5):757–64.

135. *Kamarajan P, Chao CC.* UV-induced apoptosis in resistant HeLa cells. *Biosci Rep.* 2000;**20**(2):99–108.

136. *Assefa Z, Van Laethem A, Garmyn M, Agostinis P.* Ultraviolet radiation-induced apoptosis in keratinocytes: on the role of cytosolic factors. *Biochim Biophys Acta.* 2005;**1755**(2):90–106.

137. *Chainiaux F, Magalhaes JP, Eliaers F, Remacle J, Toussaint O.* UVB-induced premature senescence of human diploid skin fibroblasts. *Int J Biochem Cell Biol.* 2002;**34**(11):1331–9.

138. *Borlon C, Chretien A, Debacq-Chainiaux F, Toussaint O.* Transient increased extracellular release of H2O2 during establishment of UVB-induced premature senescence. *Ann N Y Acad Sci.* 2007;**1119:72–7.**

139. *Jee HJ, Kim HJ, Kim AJ, Bae YS, Bae SS, Yun J.* UV light induces premature senescence in Akt1-null mouse embryonic fibroblasts by increasing intracellular levels of ROS. *Biochem Biophys Res Commun.* 2009;**383**(3):358–62.

140. *Latonen L, Taya Y, Laiho M.* UV-radiation induces dose-dependent regulation of p53 response and modulates p53-HDM2 interaction in human fibroblasts. *Oncogene.* 2001;**20**(46):6784–93.

141. *Bertrand-Vallery V, Boilan E, Ninane N, Demazy C, Friguet B, Toussaint O, Poumay Y, Debacq-Chainiaux F.* Repeated exposures to UVB induce differentiation rather than senescence of human keratinocytes lacking p16(INK-4A). *Biogerontology.* 2010;**11**(2):167–81.

142. *Chazal M, Marionnet C, Michel L, Mollier K, Dazard JE, Della Valle V, et al.* P16(INK4A) is implicated in both the immediate and adaptative response of human keratinocytes to UVB irradiation. *Oncogene.* 2002;**21**(17):2652–61.

143. *Pavey S, Conroy S, Russell T, Gabrielli B.* Ultraviolet radiation induces p16CDKN2A expression in human skin. *Cancer Res.* 1999;**59**(17):4185–9.

144. *Al-Mohanna MA, Manogaran PS, Al-Mukhalafi Z, A Al-Hussein K, Aboussekhra A.* The tumor suppressor p16(INK4a) gene is a regulator of apoptosis induced by ultraviolet light and cisplatin. *Oncogene.* 2004;**23**(1):201–12.

145. *Lu T, Finkel T.* Free radicals and senescence. *Exp Cell Res.* 2008;**314**(9):1918–22.

146. *Furumoto K, Inoue E, Nagao N, Hiyama E, Miwa N.* Age-dependent telomere shortening is slowed down by enrichment of intracellular vitamin C via suppression of oxidative stress. *Life Sci.* 1998;**63**(11):935–48.

147. *Chen Q, Fischer A, Reagan JD, Yan LJ, Ames BN.* Oxidative DNA damage and senescence of human diploid fibroblast cells. *Proc Natl Acad Sci U S A.* 1995;**92**(10):4337–41.

148. *Saretzki G, Murphy MP, von Zglinicki T.* MitoQ counteracts telomere shortening and elongates lifespan of fibroblasts under mild oxidative stress. *Aging Cell.* 2003;**2**(2):141–3.

149. *Oliver CN, Ahn BW, Moerman EJ, Goldstein S, Stadtman ER.* Age-related changes in oxidized proteins. *J Biol Chem.* 1987;**262**(12):5488–91.

150. *Fraga CG, Shigenaga MK, Park JW, Degan P, Ames BN.* Oxidative damage to DNA during aging: 8-hydroxy-2'-deoxyguanosine in rat organ DNA and urine. *Proc Natl Acad Sci U S A.* 1990;**87**(12):4533–7.

151. *Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, Yanai H, Fraifeld VE.* The role of DNA damage and repair in aging through the prism of Koch-like criteria. *Ageing Res Rev.* 2013;**12**(2):661–84.

152. *Allen RG, Tresini M, Keogh BP, Doggett DL, Cristofalo VJ.* Differences in electron transport potential, antioxidant defenses, and oxidant generation in young and senescent fetal lung fibroblasts (WI-38). *J Cell Physiol.* 1999;**180**(1):114–22.

153. *Lener B, Kozieł R, Pircher H, Hütter E, Greussing R, Herndler-Brandstetter D, Hermann M, Unterluggauer H, Jansen-Dürr P.* The NADPH oxidase Nox4 restricts the replicative lifespan of human endothelial cells. *Biochem J.* 2009;**423**(3):363–74.

154. *Catalano A, Rodilossi S, Caprari P, Coppola V, Procopio A.* 5-Lipoxygenase regulates senescence-like growth arrest by promoting ROS-dependent p53 activation. *EMBO J.* 2005;**24**(1):170–9.

155. *Chen QM, Bartholomew JC, Campisi J, Acosta M, Reagan JD, Ames BN.* Molecular analysis of H_2O_2-induced senescent-like growth arrest in normal human fibroblasts: p53 and Rb control G1 arrest but not cell replication. *Biochem J.* 1998;**332** (Pt 1):43–50.

156. *Duan J, Duan J, Zhang Z, Tong T.* Irreversible cellular senescence induced by prolonged exposure to H_2O_2 involves DNA-damage-and-repair genes and telomere shortening. *Int J Biochem Cell Biol.* 2005;**37**(7):1407–20.

157. *Zdanov S, Remacle J, Toussaint O.* Establishment of H_2O_2-induced premature senescence in human fibroblasts concomitant with increased cellular production of H_2O_2. *Ann N Y Acad Sci.* 2006;**1067**:210–6.

158. *Dumont P, Burton M, Chen QM, Gonos ES, Frippiat C, Mazarati JB, Eliaers F, Remacle J, Toussaint O.* Induction of replicative senescence biomarkers by sublethal oxidative stresses in normal human fibroblast. *Free Radic Biol Med.* 2000;**28**(3):361–73.

159. *Chen X, Zhang J, Fang Y, Zhao C, Zhu Y.* Ginsenoside Rg1 delays tert-butyl hydroperoxide-induced premature senescence in human WI-38 diploid fibroblast cells. *J Gerontol A Biol Sci Med Sci.* 2008;**63**(3):253–64.

160. *Moiseeva O, Mallette FA, Mukhopadhyay UK, Moores A, Ferbeyre G.* DNA damage signaling and p53-dependent senescence after prolonged beta-interferon stimulation. *Mol Biol Cell.* 2006;**17**(4):1583–92.

161. *Jeong SG, Cho GW.* Endogenous ROS levels are increased in replicative senescence in human bone marrow mesenchymal stromal cells. *Biochem Biophys Res Commun.* 2015;**460**(4):971–6.

162. *Lee AC, Fenster BE, Ito H, Takeda K, Bae NS, Hirai T, Yu ZX, Ferrans VJ, Howard BH, Finkel T.* Ras proteins induce senescence by altering the intracellular levels of reactive oxygen species. *J Biol Chem.* 1999;**274**(12):7936–40.

163. *Passos JF, Nelson G, Wang C, Richter T, Simillion C, Proctor CJ, Miwa S, Olijslagers S, Hallinan J, Wipat A, Saretzki G, Rudolph KL, Kirkwood TB, von Zglinicki T.* Feedback between p21 and reactive oxygen production is necessary for cell senescence. *Mol Syst Biol.* 2010;**6**:347.

164. *Rai P, Onder TT, Young JJ, McFaline JL, Pang B, Dedon PC, Weinberg RA.* Continuous elimination of oxidized nucleotides is necessary to prevent rapid onset of cellular senescence. *Proc Natl Acad Sci U S A.* 2009;**106**(1):169–74.

165. *von Zglinicki T.* Oxidative stress shortens telomeres. *Trends Biochem Sci.* 2002;**27**(7):339–44.

166. *Berlett BS, Stadtman ER.* Protein oxidation in aging, disease, and oxidative stress. *J Biol Chem.* 1997;**272**(33):20313–6.

167. *Meyer M, Schreck R, Baeuerle PA.* H2O2 and antioxidants have opposite effects on activation of NF-kappa B and AP-1 in intact cells: AP-1 as secondary antioxidant-responsive factor. *EMBO J.* 1993;**12**(5):2005–15.

168. *Gupta A, Rosenberger SF, Bowden GT.* Increased ROS levels contribute to elevated transcription factor and MAP kinase activities in malignantly progressed mouse keratinocyte cell lines. *Carcinogenesis.* 1999;**20**(11):2063–73.

169. *Patten DA, Lafleur VN, Robitaille GA, Chan DA, Giaccia AJ, Richard DE.* Hypoxia-inducible factor-1 activation in nonhypoxic conditions: the essential role of mitochondrial-derived reactive oxygen species. *Mol Biol Cell.* 2010;**21**(18):3247–57.

170. *Ito K, Hirao A, Arai F, Takubo K, Matsuoka S, Miyamoto K, Ohmura M, Naka K, Hosokawa K, Ikeda Y, Suda T.* Reactive oxygen species act through p38 MAPK to limit the lifespan of hematopoietic stem cells. *Nat Med.* 2006;**12**(4):446–51.

171. *Kim J, Wong PK.* Oxidative stress is linked to ERK1/2-p16 signaling-mediated growth defect in ATM-deficient astrocytes. *J Biol Chem.* 2009;**284**(21):14396–404.

172. *Russo T, Zambrano N, Esposito F, Ammendola R, Cimino F, Fiscella M, Jackman J, O'Connor PM, Anderson CW, Appella E.* A p53-independent pathway for activation of WAF1/CIP1 expression following oxidative stress. *J Biol Chem.* 1995;**270**(49):29386–91.

173. *Takahashi A, Ohtani N, Yamakoshi K, Iida S, Tahara H, Nakayama K, Nakayama KI, Ide T, Saya H, Hara E.* Mitogenic signalling and the p16INK4a-Rb pathway cooperate to enforce irreversible cellular senescence. *Nat Cell Biol.* 2006;**8**(11):1291–7.

174. *Minamino T, Mitsialis SA, Kourembanas S.* Hypoxia extends the life span of vascular smooth muscle cells through telomerase activation. *Mol Cell Biol.* 2001;**21**(10):3336–42.

175. *Sullivan R, Paré GC, Frederiksen LJ, Semenza GL, Graham CH.* Hypoxia-induced resistance to anticancer drugs is associated with decreased senescence and requires hypoxia-inducible factor-1 activity. *Mol Cancer Ther.* 2008;**7**(7):1961–73.

176. *Demidenko ZN, Zubova SG, Bukreeva EI, Pospelov VA, Pospelova TV, Blagosklonny MV.* Rapamycin decelerates cellular senescence. *Cell Cycle.* 2009;**8**(12):1888–95.

177. *Leontieva OV, Natarajan V, Demidenko ZN, Burdelya LG, Gudkov AV, Blagosklonny MV.* Hypoxia suppresses conversion from proliferative arrest to cellular senescence. *Proc Natl Acad Sci U S A.* 2012;**109**(33):13314–8.

178. * *Klimova TA, Bell EL, Shroff EH, Weinberg FD, Snyder CM, Dimri GP, Schumacker PT, Budinger GR, Chandel NS.* Hyperoxia-induced premature senescence requires p53 and pRb, but not mitochondrial matrix ROS. *FASEB J.* 2009;**23**(3): 783–94.

179. *Watson JA, Watson CJ, McCrohan AM, Woodfine K, Tosetto M, McDaid J, Gallagher E, Betts D, Baugh J, O'Sullivan J, Murrell A, Watson RW, McCann A.* Generation of an epigenetic signature by chronic hypoxia in prostate cells. *Hum Mol Genet.* 2009;**18**(19):3594–604.

180. *Wang W, Wang D, Li H.* Initiation of premature senescence by Bcl-2 in hypoxic condition. *Int J Clin Exp Pathol.* 2014;**7**(5):2446–53.

181. *Mo J, Sun B, Zhao X, Gu Q, Dong X, Liu Z, Ma Y, Zhao N, Tang R, Liu Y, Chi J, Sun R.* Hypoxia-induced senescence contributes to the regulation of microenvironment in melanomas. *Pathol Res Pract.* 2013;**209**(10):640–7.

182. *Welford SM, Giaccia AJ.* Hypoxia and senescence: the impact of oxygenation on tumor suppression. *Mol Cancer Res.* 2011;**9**(5):538–44.

183. *Blagosklonny MV.* Geroconversion: irreversible step to cellular senescence. *Cell Cycle.* 2014;**13**(23):3628–35.

184. *Collado M, Serrano M.* Senescence in tumours: evidence from mice and humans. *Nat Rev Cancer.* 2010;**10**(1):51–7.

185. *Larsson LG.* Oncogene- and tumor suppressor gene-mediated suppression of cellular senescence. *Semin Cancer Biol.* 2011;**21**(6):367–76.

186. *Chen Z, Trotman LC, Shaffer D, Lin HK, Dotan ZA, Niki M, et al.* Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. *Nature.* 2005;**436**(7051):725–30.

187. *Courtois-Cox S, Genther Williams SM, Reczek EE, Johnson BW, McGillicuddy LT, Johannessen CM, et al.* A negative feedback signaling network underlies oncogene-induced senescence. *Cancer Cell.* 2006;**10**(6):459–72.

188. *Young AP, Schlisio S, Minamishima YA, Zhang Q, Li L, Grisanzio C, Signoretti S, Kaelin WG Jr.* VHL loss actuates a HIF-independent senescence programme mediated by Rb and p400. *Nat Cell Biol.* 2008;**10**(3):361–9.

189. *Hemann MT, Narita M.* Oncogenes and senescence: breaking down in the fast lane. *Genes Dev.* 2007;**21**(1):1–5.

190. *Toledo LI, Murga M, Gutierrez-Martinez P, Soria R, Fernandez-Capetillo O.* ATR signaling can drive cells into senescence in the absence of DNA breaks. *Genes Dev.* 2008;**22**(3):297–302.

191. *Di Micco R, Fumagalli M, Cicalese A, Piccinin S, Gasparini P, Luise C, et al.* Oncogene-induced senescence is a DNA damage response triggered by DNA hyper-replication. *Nature.* 2006;**444**(7119):638–42.

192. *Bartkova J, Rezaei N, Liontos M, Karakaidos P, Kletsas D, Issaeva N, et al.* Oncogene-induced senescence is part of the tumorigenesis barrier imposed by DNA damage checkpoints. *Nature.* 2006;**444**(7119):633–7.

193. *Mallette FA, Gaumont-Leclerc MF, Ferbeyre G.* The DNA damage signaling pathway is a critical mediator of oncogene-induced senescence. *Genes Dev.* 2007;**21**(1):43–8.

194. *Vafa O, Wade M, Kern S, Beeche M, Pandita TK, Hampton GM, Wahl GM.* c-Myc can induce DNA damage, increase reactive oxygen species, and mitigate p53 function: a mechanism for oncogene-induced genetic instability. *Mol Cell.* 2002;**9**(5):1031–44.

195. *Irani K, Xia Y, Zweier JL, Sollott SJ, Der CJ, Fearon ER, Sundaresan M, Finkel T, Goldschmidt-Clermont PJ.* Mitogenic signaling mediated by oxidants in Ras-transformed fibroblasts. *Science.* 1997;**275**(5306):1649–52.

196. *Dolado I, Swat A, Ajenjo N, De Vita G, Cuadrado A, Nebreda AR.* p38alpha MAP kinase as a sensor of reactive oxygen species in tumorigenesis. *Cancer Cell.* 2007;**11**(2):191–205.

197. *Ogrunc M, Di Micco R, Liontos M, Bombardelli L, Mione M, Fumagalli M, et al.* Oncogene-induced reactive oxygen species fuel hyperproliferation and DNA damage response activation. *Cell Death Differ.* 2014;**21**(6):998–1012.

198. *Maya-Mendoza A, Ostrakova J, Kosar M, Hall A, Duskova P, Mistrik M, et al.* Myc and Ras oncogenes engage different energy metabolism programs and evoke distinct patterns of oxidative and DNA replication stress. *Mol Oncol.* 2015;**9**(3):601–16.

199. *Suram A, Kaplunov J, Patel PL, Ruan H, Cerutti A, Boccardi V, et al.* Oncogene-induced telomere dysfunction enforces cellular senescence in human cancer precursor lesions. *EMBO J.* 2012;**31**(13):2839–51.

200. *Neelsen KJ, Zanini IM, Herrador R, Lopes M.* Oncogenes induce genotoxic stress by mitotic processing of unusual replication intermediates. *J Cell Biol.* 2013;**200**(6):699–708.

201. *Aird KM, Zhang G, Li H, Tu Z, Bitler BG, Garipov A, et al.* Suppression of nucleotide metabolism underlies the establishment and maintenance of oncogene-induced senescence. *Cell Rep.* 2013;**3**(4):1252–65.

202. *Ribeiro JD, Morey L, Mas A, Gutierrez A, Luis NM, Mejetta S, et al.* ZRF1 controls oncogene-induced senescence through the INK4-ARF locus. *Oncogene.* 2013;**32**(17):2161–8.

203. *Sreeramaneni R, Chaudhry A, McMahon M, Sherr CJ, Inoue K.* Ras-Raf-Arf signaling critically depends on the Dmp1 transcription factor. *Mol Cell Biol.* 2005;**25**(1):220–32.

204. *Vogt M, Haggblom C, Yeargin J, Christiansen-Weber T, Haas M.* Independent induction of senescence by p16INK4a and p21CIP1 in spontaneously immortalized human fibroblasts. *Cell Growth Differ.* 1998;**9**(2):139–46.

205. *Zhu J, Woods D, McMahon M, Bishop JM.* Senescence of human fibroblasts induced by oncogenic Raf. *Genes Dev.* 1998;**12**(19):2997–3007.

206. *Uhrbom L, Nistér M, Westermark B.* Induction of senescence in human malignant glioma cells by p16INK4A. *Oncogene.* 1997;**15**(5):505–14.

207. *Efeyan A, Murga M, Martinez-Pastor B, Ortega-Molina A, Soria R, Collado M, Fernandez-Capetillo O, Serrano M.* Limited role of murine ATM in oncogene-induced senescence and p53-dependent tumor suppression. *PLoS One.* 2009;**4**(5):e5475.

208. *Astle MV, Hannan KM, Ng PY, Lee RS, George AJ, Hsu AK, Haupt Y, Hannan RD, Pearson RB.* AKT induces senescence in human cells via mTORC1 and p53 in the absence of DNA damage: implications for targeting mTOR during malignancy. *Oncogene.* 2012;**31**(15):1949–62.

209. *Sharpless NE, Ramsey MR, Balasubramanian P, Castrillon DH, DePinho RA.* The differential impact of p16(INK4a) or p19(ARF) deficiency on cell growth and tumorigenesis. *Oncogene.* 2004;**23**(2):379–85.

210. *Tao W, Levine AJ.* P19(ARF) stabilizes p53 by blocking nucleo-cytoplasmic shuttling of Mdm2. *Proc Natl Acad Sci U S A.* 1999;**96**(12):6937–41.

211. *Weber JD, Jeffers JR, Rehg JE, Randle DH, Lozano G, Roussel MF, Sherr CJ, Zambetti GP.* p53-independent functions of the p19(ARF) tumor suppressor. *Genes Dev.* 2000;**14**(18):2358–65.

212. *Haferkamp S, Scurr LL, Becker TM, Frausto M, Kefford RF, Rizos H.* Oncogene-induced senescence does not require the p16(INK4a) or p14ARF melanoma tumor suppressors. *J Invest Dermatol.* 2009;**129**(8):1983–91.

213. *Ohtani N, Zebedee Z, Huot TJ, Stinson JA, Sugimoto M, Ohashi Y, Sharrocks AD, Peters G, Hara E.* Opposing effects of Ets and Id proteins on p16INK4a expression during cellular senescence. *Nature.* 2001;**409**(6823):1067–70.

214. *Lin AW, Barradas M, Stone JC, van Aelst L, Serrano M, Lowe SW.* Premature senescence involving p53 and p16 is activated in response to constitutive MEK/MAPK mitogenic signaling. *Genes Dev.* 1998;**12**(19):3008–19.

215. *Michaloglou C, Vredeveld LC, Soengas MS, Denoyelle C, Kuilman T, van der Horst CM, Majoor DM, Shay JW, Mooi WJ, Peeper DS.* BRAFE600-associated senescence-like cell cycle arrest of human naevi. *Nature.* 2005;**436**(7051):720–4.

216. *Dhomen N, Reis-Filho JS, da Rocha Dias S, Hayward R, Savage K, Delmas V, Larue L, Pritchard C, Marais R.* Oncogenic Braf induces melanocyte senescence and melanoma in mice. *Cancer Cell.* 2009;**15**(4):294–303.

217. *Vredeveld LC, Possik PA, Smit MA, Meissl K, Michaloglou C, Horlings HM, et al.* Abrogation of BRAFV600E-induced senescence by PI3K pathway activation contributes to melanomagenesis. *Genes Dev.* 2012;**26**(10):1055–69.

218. *Collado M, Gil J, Efeyan A, Guerra C, Schuhmacher AJ, Barradas M, Benguría A, Zaballos A, Flores JM, Barbacid M, Beach D, Serrano M.* Tumour biology: senescence in premalignant tumours. *Nature.* 2005;**436**(7051):642.

Особливості молекулярних механізмів передчасного клітинного старіння, які залежать від стрес-фактору, що індукує старіння

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Клітинне старіння є відповіддю клітини на стрес у вигляді перманентного арешту проліферації, супроводжуваного комплексом фенотипічних змін. Найбільш важливими ознаками клітинного старіння є відсутність синтезу ДНК, збільшення активності асоційованої зі старінням β-галактозидази і збільшення експресії інгібіторів циклін-залежних кіназ. Ці універсальні маркери клітинного старіння характерні також і для інших типів арешту проліферації клітин. Поряд з універсальними маркерами клітинне старіння має додаткові характеристики, які більшою мірою залежать від фактора, що індукує старіння та / або типу клітин. У цьому огляді ми розглянемо основні характеристики і механізми, індукції клітинного старіння, приділивши особливу увагу залежних від стрес-фактора відмінностям активуються при клітинному старінні сигнальних каскадів.

К л ю ч о в і с л о в а: клітинне старіння, теломери, пошкодження ДНК, опромінення, активні форми кисню, онкогени

Особенности молекулярных механизмов преждевременного клеточного старения, зависящие от индуцирующего старение стресс-фактора.

Надежда В. Петрова, Артем К. Величко, Наталья В. Петрова, Сергей В. Разин, Омар Л. Кантидзе

Клеточное старение является клеточным ответом на стресс в виде перманентного ареста пролиферации, сопровождаемого комплексом фенотипических изменений. Наиболее важными признаками клеточного старения являются отсутствие синтеза ДНК, увеличение активности ассоциированной со старением β-галактозидазы и увеличение экспрессии ингибиторов циклин-зависимых киназ. Эти универсальные маркеры клеточного старения характерны также и для других типов ареста пролиферации клеток. Наряду с универсальными маркерами клеточное старение имеет дополнительные характеристики, которые в большей степени зависят от индуцирующего старение фактора и/или типа клеток. В этом обзоре мы рассмотрим основные характеристики и механизмы, участвующие в индукции клеточного старения, уделив особое внимания зависящим от стресс-фактора различиям активируемых при клеточном старении сигнальных каскадов.

К л ю ч е в ы е с л о в а: клеточное старение, теломеры, повреждения ДНК, облучение, активные формы кислорода, онкогены