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

Nadezhda V. Petrova[1], Artem K. Velichko[1], Natalia V. Petrova[1],
Sergey V. Razin[1,2], Omar L. Kantidze[1]

1 Institute of Gene Biology, Russian Academy of Sciences
34/5, Vavilova Str., Moscow, Russian Federation, 119334

[2] M. V. Lomonosov Moscow State University
Leninskie Gory, 1/12, Moscow, Russian Federation, 119991
sergey.v.razin@usa.net and kantidze@gmail.com

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.

Keywords: 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 subsequent 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

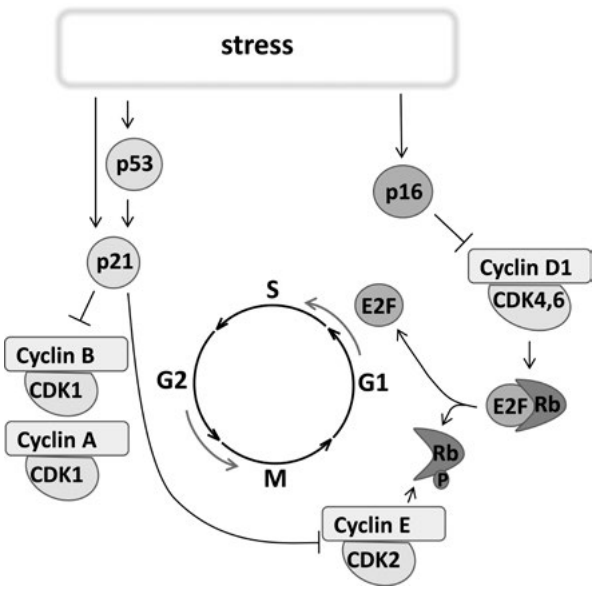

Fig. 1. Simplified model of the stress-induced inhibition of the cell cycle progression (see the text for further details)

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

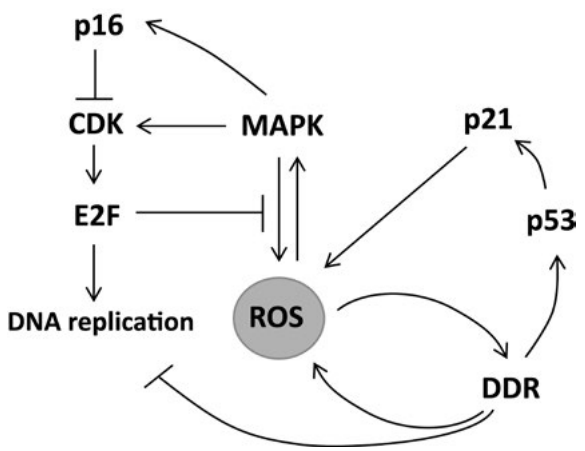

Fig. 2. Production of ROS may be enhanced by the functioning of a positive feedback loop between the MAPK and DDR signaling pathways and the action of the ROS (see the text for further details)

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

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

Надєжда В. Петрова, Артем К. Величко,
Наталія В. Петрова, Сергій В. Разін, Омар Л. Кантидзе

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 циклин-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 уваги залежних від стрес-фактора відмінностям активуються при клітинному старінні сигнальних каскадів.

Ключові слова: 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.

Ключевые слова: клеточное старение, теломеры, повреждения ДНК, облучение, активные формы кислорода, онкогены

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