ISSN 0006-2979, Biochemistry (Moscow), 2025, Vol. 90, No. 12, pp. 1883-1896 © The Author(s) 2025. This article is an open access publication.
Published in Russian in Biokhimiya, 2025, Vol. 90, No. 12, pp. 1981-1996.

REVIEW

Antibiotics and Cellular Senescence: An Unexplored Territory

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Received August 26, 2025
Revised November 17, 2025
Accepted November 27, 2025

Abstract—Antibiotics are certainly the most important agents in the fight against human and animal bacterial infections. Widespread use of antibiotics has a positive impact on the treatment of infectious diseases but may be accompanied by serious side effects. Clinical aspects of these side effects are well understood, but nonspecific molecular targets are not fully recognized. It is generally known that many antibiotics can damage mitochondria, intracellular organelles responsible for aerobic metabolism as well as regulating a number of important processes, including cellular redox balance and inflammatory responses. Mitochondrial dysfunction commonly leads to the development of oxidative stress and inflammation, which are known stimuli of cellular senescence. On the other hand, the same stimuli could induce death of senescent cells. Thus, mitotoxic antibiotics could influence both the cellular senescence process and elimination of senescent cells. The effect of antitumor antibiotics on the induction of cell aging has been studied in detail, but the effect of antibacterial antibiotics on this process is still essentially unknown. This review aims to draw attention of the researchers to the possibility of accelerated cellular aging induced by common antibacterial antibiotics and to discuss potential mechanisms of this process.

DOI: 10.1134/S0006297925602758

Keywords: antibiotics, side effects, cellular senescence, mitochondria, reactive oxygen species

INTRODUCTION

Since their discovery, antibiotics have remained indispensable tools in the fight against bacterial infections, dramatically reducing infection-related mortality and contributing substantially to the increased life expectancy worldwide. However, their use is accompanied by various non-specific effects, physiological features of which are well documented [1]. At least part of these side effects could be attributed to the evolutionary relationship between bacteria and mitochondria, which originated from the ancient alphaproteobacteria [2]. Consequently, many antibiotics that target bacterial replication or translation also induce mitochondrial dysfunction [3]. The downstream consequences of mitochondrial dysfunction, such as oxidative stress and inflammation, could, in turn, trigger cell cycle arrest and drive cells into a state of cellular senescence (CS).

Although numerous individual studies and reviews have addressed antibiotic side effects and the phenomenon of CS, the relationship between these two events remains largely unexplored. The primary exception is antitumor antibiotics, which are known to induce CS through activation of the cellular DNA damage response. This review briefly outlines current understanding of the mechanisms of CS development, primary and non-specific targets of antibacterial antibiotics, and analyzes the limited available evidence regarding their ability to promote CS or eliminate senescent cells in human and animal systems.

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Cellular aging (senescence) is defined as a stable cell cycle arrest accompanied by characteristic phenotypic changes [4] (Fig. 1). CS is intimately involved in the processes such as embryogenesis, tissue regeneration, suppression of carcinogenesis, and aging. As an antitumor mechanism, CS prevents proliferation of the potentially cancerous cells. Activation of the tumor suppressor pathways p53/p21CIP1 and p16INK4A/pRB plays a central role in the development of CS [5, 6].

Aging cells remain viable, but their metabolic and transcriptomic activities change, and they develop a complex secretory phenotype (senescence-associated secretory phenotype, SASP). This phenotype is characterized by the synthesis of cytokines and inflammatory mediators, proteases, and growth factors (such as IL-1α, IL-1β, IL-6, IL-8, and MMP) [7]. Senescent cells can be eliminated by immune cells, this process contributes to the tissue remodeling and regeneration. However, under certain conditions, aging cells are not completely removed, which contributes to the development of pathology [8]. Factors secreted by the senescent cells can affect neighboring cells in a paracrine manner and disturb normal tissue functions.

Cellular aging occurs in response to various endogenous and exogenous stimuli. There are two main types of CS: replicative and stress-induced (Fig. 1). In the replicative aging, a cell that has divided many times with shortened telomeres loses its ability to proliferate, leading to the complete halt in the cell cycle [9]. The stress-induced aging is caused by a wide range of factors, such as mitogenic signals, oncogene activation, radiation, oxidative and genotoxic stress, epigenetic changes, chromatin disorganization, proteostasis disruption, mitochondrial dysfunction, inflammatory responses, tissue damage signals, chemotherapeutic agents, and nutrient deprivation [10, 11]. Aging caused by DNA damage is triggered by a wide range of chemical compounds, as well as ionizing or UV radiation. Depending on the intensity of DNA damage, the cell may die by apoptosis or progress to CS [12]. More than fifty compounds have been identified [13] that induce cellular aging, with the specific mechanism of cellular aging development varying for different groups of substances.

The most important physiologically significant signs of CS are increase in the cell size, increase in the activity of senescence-associated β-galactosidase (SA-β-gal), accumulation of autofluorescent granules, and SASP [13] (Fig. 1). The increased autofluorescence and the SA-β-gal activity result from accumulation

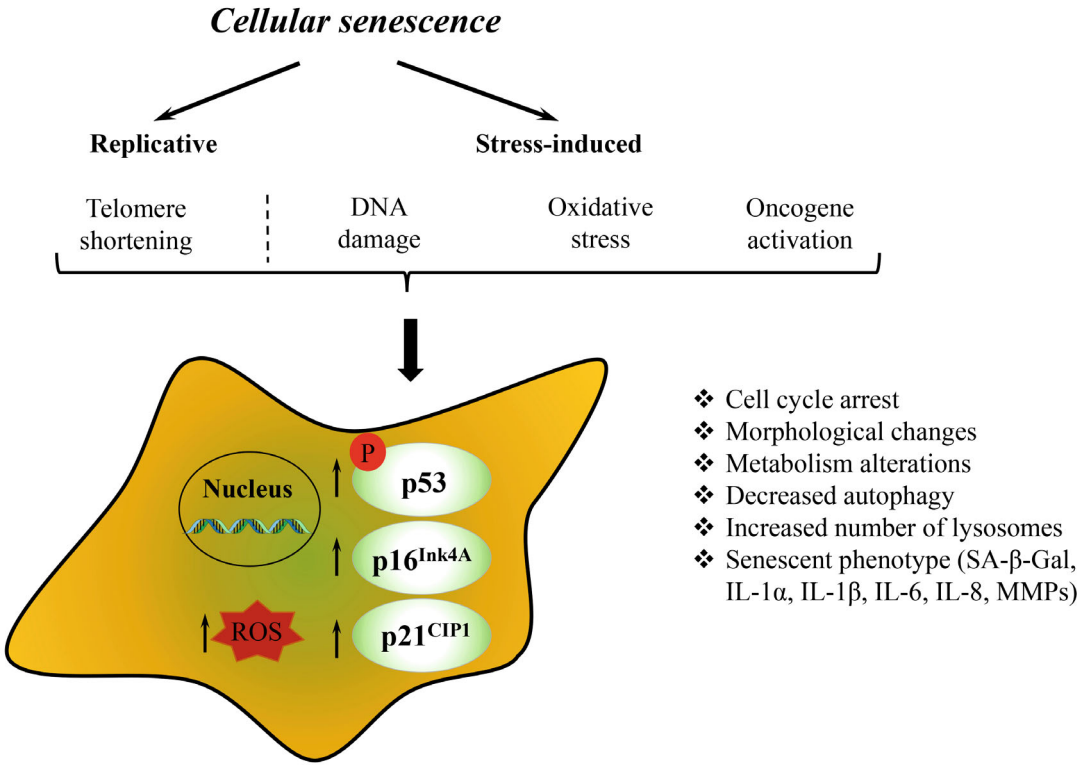

Fig. 1. Main pathways of cellular senescence (CS) induction and characteristics of senescent cells. ROS, reactive oxygen species; p53, p16Ink4a, p21CIP1, senescence protein markers; SA-β-Gal, senescence-associated beta-galactosidase; IL-1α, interleukin-1α; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; MMPs, matrix metalloproteinases. Details are provided in the text.

of the excessive amounts of lysosomal components in cells. To date, dozens of phenotypes of stress-induced CS have been described, which partially overlap with each other [14]. These aging states can differ significantly from each other and from the phenotype of replicative aging. At the same time, it is still unclear whether the cell cycle arrest constitutes the "true" CS. Essential characteristics of this "true" CS are also undefined.

ANTIBIOTICS: CLASSIFICATION AND MECHANISM OF ACTION

Antibiotics constitute a heterogeneous group of compounds belonging to various classes of chemical substances, each characterized by a unique structure and mechanism of action. Functionally, they are generally categorized into two types: bacteriostatic antibiotics, which inhibit growth and reproduction of microorganisms, and bactericidal antibiotics, which kill bacterial cells. Although the term antibiotics originally referred exclusively to the substances of natural origin, it is now used more broadly to include semi-synthetic and fully synthetic antimicrobial agents [15]. Based on the spectrum of their activity, antibiotics may be classified as narrow-spectrum, targeting specific groups of bacteria (e.g., vancomycin against Gram-positive organisms), or broad-spectrum, acting against a wide range of bacterial species (e.g., tetracyclines, cephalosporins). Furthermore, antibiotics can be categorized according to their chemical structure into classes such as β-lactams, aminoglycosides, macrolides, tetracyclines, phenicols, glycopeptides, polymyxins, lincosamides, fluoroquinolones, and rifamycins, among others [16].

The primary targets of antibiotic action in bacteria include synthesis of the cell wall, proteins, nucleic acids, mycolic acids, and folic acid (Table 1) [15, 17]. The table also lists ionophores, such as monensin, lasalocid, and salinomycin, which disrupt intracellular ion homeostasis [18]. These ionophores are used in veterinary medicine.

Several bacterial-derived compounds that are also classified as antibiotics are widely used in cancer therapy. These include the anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin), as well as bleomycin, dactinomycin, and mitomycin. Their anticancer activity is mediated through multiple mechanisms, including: (i) DNA alkylation (e.g., certain anthracyclines); (ii) DNA intercalation (doxorubicin, daunorubicin, actinomycin D); (iii) inhibition of topoisomerase II (doxorubicin); (iv) induction of DNA strand breaks (bleomycin) [19]. The resulting DNA damage leads to cell cycle arrest and ultimately to tumor cell death [20].

Table 1. Mechanism of action of the main groups of antibiotics

Classification of antibiotics by mechanism of action	
Cell wall synthesis inhibitors	• penicillins • cephalosporins • glycopeptides • β-lactamase inhibitors • carbapenems • β-lactams • polypeptides
Protein synthesis inhibitors	30S Subunit inhibitors • aminoglycosides • tetracyclines 50S Subunit inhibitors • macrolides • phenicols • lincosamides • oxazolidinone • streptogramins
DNA synthesis inhibitors	• fluoroquinolones • 5-nitroimidazoles
Folic acid synthesis inhibitors	• sulfonamides
Ionophores that disrupt ion conductivity	• carboxylic polyethers • linear and cyclic peptides

NON-SPECIFIC TARGETS OF ANTIBIOTICS

Being small molecules (400-1200 Da), antibiotics have good bioavailability and effectively block vital bacterial functions in the tissues of the infected organism. On average, the low-molecular-weight compounds can bind to 6-11 off-target molecules inside the cell in addition to their primary target [21]. Antibiotics can cause side effects of varying severity, which, according to the current data, are partly due to their effect on the human microbiota and partly to their interaction with non-specific cellular targets [22]. Clinical aspects of antibiotic side effects have been studied in great detail [1, 23], but nonspecific intracellular interactions are only partially understood.

As noted above, many antibiotic-associated side effects arise from the evolutionary relationship between mitochondria and bacteria; mitochondria are currently believed to have originated from the ancient Alphaproteobacteria [2]. Consequently, numerous antibiotics designed to target bacterial replication or translation also exhibit varying degrees of mitochondrial toxicity (Table 2), although not all have been experimentally shown to interact with nonspecific

Table 2. Nonspecific mitochondrial targets of selected antibiotics and their associated side effects

Antibiotics	Potential antibiotic target in mitochondria	Effect at the cellular level	Side effects at the organismal level	References
Oxazolidinones	50S ribosomal subunit	inhibition of megakaryocyte maturation	thrombocytopenia, anemia	[28]
		reduced COX-II production in PBMCs	hyperlactatemia	[29]
		mitochondrial dysfunction in optic nerve cells	optic neuropathy	[30, 31]
Lincosamides	50S ribosomal subunit	neuronal apoptosis	neurotoxicity	[32]
Phenicols	50S ribosomal subunit	decreased transferrin receptor expression and ferritin synthesis	sideroblastic anemia	[33]
		disruption of mitochondrial protein synthesis and subsequent impairment of erythroid cell development	aplastic anemia	[34]
Macrolides	50S ribosomal subunit	neuronal apoptosis	neurotoxicity	[32]
		cardiomyocyte apoptosis	cardiotoxicity	[35]
		hepatocyte oxidative stress	hepatotoxicity	[35, 36]
Aminoglycosides	30S ribosomal subunit	disruption of mitochondrial protein synthesis in cochlear cells	ototoxicity	[36, 37]
		renal tubular cell mitochondrial dysfunction	nephrotoxicity	[38, 39]
Tetracyclines	30S ribosomal subunit	mitochondrial dysfunction and nerve cell death	neurotoxicity	[32]
Fluoroquinolones	gyrase/topoisomerase	mitochondrial dysfunction and oxidative stress in tenocytes	tendinopathy	[40, 41]
		oxidative stress in chondrocytes	chondrotoxicity	[42]
		mitochondrial dysfunction and oxidative stress in Müller cells	retinopathy	[43]
		decreased GLUT1 expression	dysglycemia	[44]
Nitroimidazoles	gyrase/topoisomerase	ROS-independent neuronal death	neurotoxicity	[32]

mitochondrial targets [3]. Principal mechanisms underlying this toxicity include inhibition of respiratory chain complexes, uncoupling of oxidative phosphorylation, disruption of mitochondrial protein transport, and suppression of key reactions within the tricarboxylic acid cycle [24]. Comprehensive discussions of these nonspecific mitochondrial effects can be found in several recent review articles [2, 25-27].

In particular, proteins of the mitochondrial 50S ribosomal subunit display high degree of homology to their bacterial counterparts, which explains why antibiotics targeting the prokaryotic 50S subunit could also impair mitochondrial translation [45]. Indeed, all classes of antibiotics listed in Table 1 that act on the 50S subunit (except clindamycin) have been shown to inhibit not only bacterial, but also mitochondrial

protein synthesis [46-51]. For example, XL2, a member of the oxazolidinone class, suppresses mitochondrial translation by binding to the same A-site on the ribosome as it does in bacterial cells [52].

In addition to targeting the 50S subunit, some antibiotics also act on the mitochondrial 30S ribosomal subunit, thereby inhibiting mitochondrial translation. Adverse effects of certain antibiotics appear to depend on structural features of the mitochondrial 30S subunit. For example, mutations in the mitochondrial 12S rRNA gene (1555A>G and 1494C>T) are associated with the significantly increased risk of aminoglycoside-induced ototoxicity [53, 54]. These mutations are thought to render the secondary structure of mitochondrial 12S rRNA, a component of the 30S subunit, more similar to the corresponding region of the bacterial 16S rRNA, which constitutes a therapeutic target of aminoglycosides [37, 55, 56].

Doxycycline, a member of the tetracycline class, induces a "mitonuclear imbalance" characterized by disruption of the stoichiometric ratio between mitochondrial and nuclear genomes that encode electron transport chain (ETC) proteins [57]. This imbalance subsequently leads to mitochondrial fragmentation and impaired respiratory function [57].

In addition to the impairing mitochondrial replication, fluoroquinolone antibiotics also disrupt mitochondrial protein synthesis and decrease relative amount of mitochondrial DNA (mtDNA) [58, 59]. Proteomic analyses in the eukaryotic cell line HEK-293 have identified several additional intracellular targets of fluoroquinolones. Among these is NUDT1, an enzyme involved in protecting cells from oxidative stress by hydrolyzing oxidized nucleotides. Treatment with ciprofloxacin or levofloxacin reduces NUDT1 levels, thereby lowering cellular resistance to the fluoroquinolone-induced oxidative stress [60]. Several mitochondrial proteins were also identified as targets, including AIFM1 – a regulator of cell death and a mediator of metabolite transport across the inner mitochondrial membrane. Ciprofloxacin has been shown to bind AIFM1, resulting in dysfunction of respiratory chain complexes I and IV. Moreover, both ciprofloxacin and levofloxacin inhibit IDH2 (isocitrate dehydrogenase 2), further contributing to ETC impairment [60].

Antibiotics that do not target bacterial replication or translation, such as vancomycin and ceftriaxone (inhibitors of bacterial cell wall synthesis) also exhibit nonspecific interactions within host tissues. For example, vancomycin can bind to elastin, a structural protein of the vessel wall, promoting formation of vancomycin aggregates that exert toxic effects on the endothelial cells [61]. Ceftriaxone, a cephalosporin antibiotic, has been shown to interact with Aurora B kinase, a key regulator of cell cycle and tumor progression. This unexpected interaction highlights the potential for exploring anticancer properties of ceftriaxones [62].

ANTIBIOTICS AND CELLULAR SENESCENCE

Antibiotics used in cancer therapy. As noted above, several antibiotics are employed as antitumor agents and, by definition, have the capacity to halt the cell cycle and induce cellular senescence. These compounds damage cellular DNA, activate the DNA damage response, and generate oxidative stress, all of which contribute to the onset and progression of cellular senescence.

Anthracyclines form cleavable DNA complexes, inhibit topoisomerase II activity, and induce oxidative stress, collectively disrupting both transcription and DNA replication [63]. They also trigger mitochondrial dysfunction by inhibiting components of the respiratory chain, promoting mitochondrial iron accumulation, and increasing production of reactive oxygen species (ROS) [64]. Capacity of doxorubicin and other anthracyclines to induce cellular senescence is well documented; both their mitochondrial and genotoxic effects, accompanied by oxidative stress, contribute to this outcome [65, 66]. Notably, the doxorubicin-induced senescence could proceed through mechanisms that are either p53-dependent or p53-independent [67]. Importantly, anthracyclines have been shown to induce cellular senescence not only *in vitro* but also in animal models [68, 69].

Bleomycin induces the genomic DNA strand breaks [70] and promotes mitochondrial dysfunction, both of which contribute to the development of cellular senescence [71]. It triggers a senescent phenotype characterized by the increased numbers of SA-β-gal positive cells, morphological alterations, elevated lysosomal content, and reduced proliferative capacity in the A549 lung adenocarcinoma cells, as well as in the primary alveolar epithelial cells isolated from the rats with bleomycin-induced pulmonary fibrosis [72]. In the lung tissue of these animals, elevated levels of γH2AX-positive cells, activation of p21, and emergence of SASP were also observed [73]. Furthermore, two bleomycin derivatives, boanmycin and boningmycin, have likewise been reported to induce cellular senescence [74, 75].

Dactinomycin (actinomycin D), an inhibitor of RNA synthesis in both prokaryotic and eukaryotic cells, has been shown to induce cellular senescence [76, 77]. In the human mesenchymal stem cells, dactinomycin treatment leads to the increased SA-β-gal activity and SASP development [77]. Senescence induction has also been observed in the OCI-AML3 acute myeloid leukemia cells carrying the mutant form of

NPM1 gene (NPM1c), where it is accompanied by mitochondrial stress, including mitochondrial fragmentation and elevated ROS production [76]. Moreover, the conditioned medium from the dactinomycin-treated cells was found to reduce mitochondrial inner membrane potential ($\Delta\Psi m$) and increase ROS levels in the recipient cells [78].

Mitomycin C induces formation of inter- and intrastrand DNA crosslinks between guanine residues, thereby inhibiting both DNA replication and transcription [79]. It also damages mtDNA [80], thus contributing to mitochondrial dysfunction [81]. In the human dermal fibroblasts, mitomycin C triggers cellular senescence, characterized by the increased SA-β-gal activity, cell-cycle arrest, development of the senescence-associated secretory phenotype (SASP), and elevated ROS levels [82]. *In vivo*, mitomycin C has likewise been shown to induce cellular senescence, as demonstrated in the rabbit trabeculectomy model [83].

The promising antitumor ionophore antibiotic salinomycin, which also possesses antibacterial properties, not only induces DNA damage but also promotes lysosomal iron accumulation and oxidative stress. These effects lead to the cell-cycle arrest and development of cellular senescence in the MDA-MB-231 breast cancer cells [84, 85]. Interestingly, despite its pro-senescence activity, salinomycin is also capable of inducing apoptosis in various human tumor cell types, including MDA-MB-231 cells [84, 86, 87].

The relatively rare antitumor antibiotic lidamycin also appears to induce cellular senescence. Treatment of the BEL-7402 and MCF-7 cells, with lidamycin leads to the increased cell size and higher proportion of the SA-β-gal-positive cells [88]. Studies with the BEL-7402 cells further demonstrate that lidamycin could trigger senescence and mitotic catastrophe either in parallel or sequentially [89]. Reduction in the telomerase activity and decreased expression of EZH2 are thought to play key roles in the lidamycin-induced senescence [89, 90].

Antibacterial antibiotics. Influence of antibiotics not traditionally used in cancer therapy on the development of cellular senescence remains poorly understood. Chloramphenicol, an inhibitor of both bacterial and mitochondrial protein synthesis, has been shown to suppress the mitomycin C-induced apoptosis while increasing the p21 expression and the number of SA-β-gal-positive cells [50]. Similar senescence-promoting effects have been observed with other protein synthesis inhibitors, including doxycycline, clindamycin, and minocycline [50]. Cephalexin, a cephalosporin antibiotic, does not induce senescence on its own; however, it enhances senescence in the cells exposed to ionizing radiation, indicating potential radiosensitizing properties [91].

It can be hypothesized that antibiotics inducing mitochondrial dysfunction could, under certain conditions, promote the development of cellular senescence (Fig. 2). Mitochondrial dysfunction is known to trigger inflammatory responses through the release of mitochondrial damage-associated molecular patterns (DAMPs), including mitochondrial DNA, mitochondrial RNA, and N-formylmethionine-containing proteins [92, 93]. Inflammation, in turn, is a well-established driver of cellular senescence (Fig. 1). Moreover, mitochondrial dysfunction is almost invariably accompanied by oxidative stress resulting from the impaired redox processes [94, 95], which further contributes to the senescence induction [96] (Figs. 1 and 2).

Antibiotics capable of inducing cellular senescence include oxazolidinones, which impair mitochondrial function, cause cell cycle arrest, and increase proportion of the SA-β-gal-positive cells [97, 98]. Similar to salinomycin, oxazolidinones could simultaneously trigger both senescence and apoptosis, as demonstrated in the DU145 prostate cancer cells [98]. A recent review [99] summarizes evidence supporting potential use of oxazolidinones and their derivatives as antitumor agents. In addition, the bacteriostatic veterinary antibiotics amoxicillin and chlortetracycline have been shown to inhibit cell proliferation [100].

Incubation of glioblastoma cells with the fluoroquinolone ciprofloxacin induced CS. When exposure was limited to 10 days, this senescent state was reversible: after ciprofloxacin was removed from the medium, the cells resumed proliferation after a 2-3-day lag [101]. In contrast, treatment for 15 days or longer resulted in irreversible senescence. Reversibility of the ciprofloxacin-induced senescence was shown to depend on RelA (p65), a subunit of the NF-κB complex [101]. However, it remains unclear how ciprofloxacin and other fluoroquinolones influence senescence in non-tumor cell lines or in animal models.

Antibiotics as senolytics. Accumulation of senescent cells is known to impair functions of organs and tissues, in part due to the chronic inflammation driven by SASP. The use of senolytics, agents that selectively eliminate senescent cells, has been shown to restore lost or compromised functions [102]. Senolytics can be broadly divided into two major categories: the first targets pro-survival pathways in the senescent cells, thereby promoting their apoptosis; the second amplifies existing cellular stresses within senescent cells, triggering in addition to apoptosis alternative forms of cell death such as necrosis or ferroptosis [102].

In addition to the well-established senolytics such as combination of quercetin with dasatinib [103, 104], senolytic properties have also been found in several antibiotics. Although the mechanisms underlying the senolytic activity of most antibiotics remain

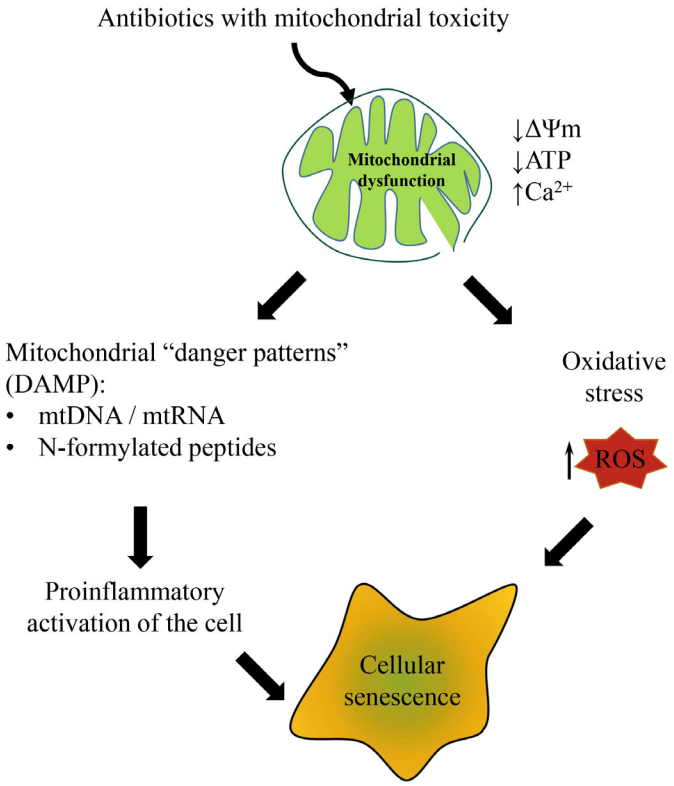

Fig. 2. Possible pathways of cell senescence induction by antibiotics. Abbreviations: ↓ΔΨm, decrease in mitochondrial transmembrane potential; ↓ATP, decrease in ATP level; ↑Ca^{2+}, increase in calcium ion concentration; ROS, reactive oxygen species. Details are given in the text.

largely unexplored, available evidence indicates that these compounds fall into the second major category of senolytics: they enhance pre-existing stresses in the senescent cells, primarily through mitochondrial disruption and/or interference with autophagy pathways.

The ionophore antibiotic nigericin has been shown to exert a multifaceted senolytic effect by depolarizing both the plasma membrane and the inner mitochondrial membrane, promoting cytoplasmic acidification, and inhibiting autophagy. Together, these disruptions destabilize cellular homeostasis and ultimately lead to the death of senescent cells [105]. Notably, targeting any one of these processes individually was insufficient to produce a senolytic effect.

In the study using the A549 cell-based aging model induced by alisertib and CFI-400945, addition of the ionophore salinomycin triggered mitochondrial dysfunction and oxidative stress, leading to elimination of the SA-β-gal positive cells through PANoptosis – a coordinated activation of pyroptosis, apoptosis, and necroptosis [106]. Effects of salinomycin resembled those observed upon knockdown of the *SLC25A23* gene encoding a mitochondrial carrier protein that facilitates Ca^{2+} uptake [106].

Senolytic activity has also been identified among the macrolide antibiotics. Azithromycin and roxithromycin were shown to exert senolytic effects in the MRC5 and BJ fibroblasts in the bromodeoxyuridine-induced senescence model, with azithromycin demonstrating greater selectivity toward the senescent cells [107]. This senolytic action appears to be mediated, at least in part, by the induction of autophagy, although azithromycin exhibited a concentration-dependent, bidirectional influence on mitochondrial respiration. Azithromycin also displayed senolytic properties in the "aged" endometrial stromal cells isolated from the patients with ovarian endometriosis [108]. Interestingly, erythromycin showed no senolytic effect in one study [107], yet demonstrated senolytic activity in another, that used a hydrogen peroxide-induced senescence model in the BEAS-2B epithelial cells [109]. Roxithromycin also exhibited senolytic effects in the WI-38 lung fibroblasts in the bleomycin-induced senescence model [110].

Several antibiotics that inhibit bacterial protein synthesis have also demonstrated senolytic activity. The veterinary antibiotic valnemulin, for example, reduced proportion of the senescent cells in the intestinal tissue of mice with experimentally induced ulcerative colitis [111]. Doxycycline, a member of the tetracycline class, exhibited senolytic effects in the mouse embryonic fibroblasts derived from the Hutchinson–Gilford progeria mice model [112].

Chloramphenicol was shown to prevent the 5-fluorouracil-induced senescence by activating autophagy [113]. Interestingly, however, another study reported that both chloramphenicol and doxycycline increased the number of SA-β-gal positive cells and elevated the p21 protein levels, suggesting context-dependent effects on cellular senescence [50].

CONCLUSION

The ability of antitumor antibiotics to induce stable cell-cycle arrest and cellular senescence both *in vitro* and *in vivo* has long been recognized and is supported by numerous experimental studies. A classic example is the anthracycline doxorubicin, which induces persistent DNA damage, activates the p53/p21 signaling pathway, and triggers hallmark senescence phenotypes such as SA-β-gal activity and SASP. The doxorubicin-induced senescent cells have also been shown to contribute to the late adverse effects of chemotherapy [114].

Interestingly, the same or structurally similar agents can exhibit opposing activities – promoting senescence under some conditions while acting as senolytics under others. A notable example is the antibiotic salinomycin: several studies have shown that it induces hallmark features of CS in tumor cells (e.g., increased SA-β-gal activity and elevated p21), whereas more recent findings demonstrate that it can also function as a senolytic, triggering PANoptosis in the pre-existing senescent cells [84, 106]. This context-dependent duality underscores complexity of the antibiotic-mediated stress responses and suggests potential for the two-stage cancer therapeutic strategies in which the chemotherapy-induced tumor senescent cells are subsequently cleared using senolytics [106].

Mechanistically, many antibiotics, particularly bactericidal ones such as fluoroquinolones, aminoglycosides, and certain β-lactams, exert mitotoxic effects on eukaryotic cells, leading to mtDNA damage, impaired mitochondrial energy metabolism, and increased ROS production [115]. These disturbances are closely linked to activation of the cellular senescence programs, suggesting that the antibiotic-induced mitotoxicity may underlie their pro-senescence side effects. However, prevalence and biological significance of these effects *in vivo* remain poorly understood. To date, there is virtually no direct evidence demonstrating causal relationship between the antibiotic exposure and accumulation of the senescent cells in human tissues.

These knowledge gaps carry important clinical implications. Long-term side effects of antibiotic use (persistent changes in the microbiota, metabolic and immune shifts, musculoskeletal risks, etc.) have been well documented in both epidemiological and experimental studies. It is plausible that some of these lasting consequences may, in part, stem from the antibiotic-induced cellular senescence in critical cell populations, including fibroblasts, endothelial cells, and other mesenchymal-derived cells. This hypothesis warrants further focused investigation.

Taken together, the evidence suggests that almost all antibiotics exhibiting pronounced mitotoxicity or capacity to induce DNA stress in eukaryotic cells may, under certain conditions, such as specific dosages, exposure durations, cellular targets, and microenvironmental contexts, influence cellular aging processes. This highlights several important directions for systematic investigation: (i) comprehensive screening of antibiotic molecules for pro-senescence and senolytic activities across the diverse primary and tissue-specific cellular models; (ii) determination of threshold concentrations and temporal windows at which the pro-senescence effects transition into overt cytotoxicity; (iii) *in vivo* studies aimed at detecting and mapping senescent cell accumulation following clinically relevant antibiotic regimens; and (iv) assessment of the contribution of antibiotic-induced cellular senescence to the long-term clinical outcomes, as well as exploration of whether these effects could be mitigated using senomorphics or senolytics.

Convergence of the experimental evidence on mitotoxic and pro-senescence effects of multiple antibiotics with clinical observations of long-term adverse outcomes provides a strong rationale for the targeted investigations into the role of cellular senescence in antibiotic toxicity. Systematic examination of this issue would not only deepen our understanding of the fundamental mechanisms underlying antibiotic-associated side effects but could also open new strategies for their prevention and treatment. Such efforts may ultimately support the design of combination approaches “antibiotic + senolytics/senomorphics”, when it is safe and supported by evidence.

Abbreviations

CS	cellular senescence
IL	interleukin
ROS	reactive oxygen species
SA-β-gal	senescence-associated beta-galactosidase
SASP	senescence-associated secretory phenotype

Acknowledgments

The authors would like to thank Evgeniy Sergeevich Egorov for inspiration, supply of information, and invaluable help in the work.

Contributions
R. A. Zinovkin – concept of the paper and writing the text. N. D. Kondratenko – writing and editing of the text.

Funding
The work was financially supported by Russian Science Foundation (project no. 25-24-00307).

Ethics approval and consent to participate
This work does not contain any studies involving human and animal subjects.

Conflict of interest
The authors of this work declare that they have no conflicts of interest.

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