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Senescent Cells and Their Role in Histogenesis

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ABSTRACT

Aging, or senescence (from Latin *senex*—old man), is a biological process characterized by the gradual degradation of organs and systems at various hierarchical levels of structural organization. Currently, the concept of cellular senescence is the prevailing framework for understanding organismal aging. It has been demonstrated that certain cells in developing (prenatal histogenesis) and definitive tissues undergo a series of morphofunctional changes, including increased cell size; disruption of the nuclear envelope; formation of distinct heterochromatin foci; acquisition of a secretory phenotype characterized by the production of proinflammatory cytokines, β-galactosidase, transforming growth factor β (TGFβ), and other factors; and mitotic arrest through the active transcription of *p16INK4A* and *p21CIP1*, genes involved in the induction of cellular senescence. It is hypothesized that such cells, referred to as senescent cells, represent an independent functional stage of cytogenesis within tissues rather than merely a transitional form between actively functioning cell lineage elements and those undergoing programmed cell death. The histogenetic significance of senescent cells in both physiological and reparative tissue regeneration, as well as their broader impact on histophysiology, remains to be fully elucidated. The pharmacologic elimination of senescent cells from tissues is an actively developing strategy in anti-aging therapy.

Keywords: senescent cells; aging; histogenesis; age-related histology; age-associated diseases.

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Сенесцентные клетки и их место в структуре гистогенеза

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АННОТАЦИЯ

Старение, или сенесценция (от лат. *senex* — старец), представляет собой биологический процесс, заключающийся в постепенной деградации частей и систем организма на различных иерархических уровнях структурной организации материи. Комплексные представления о клеточном старении сегодня являются доминирующей концепцией, описывающей процессы старения организма в целом. Показано, что некоторые клетки в составе формирующихся (пренатальный гистогенез) и дефинитивных тканей претерпевают ряд морфофункциональных изменений: увеличение в размерах; повреждение кариолеммы; образование особых участков гетерохроматина; формирование секреторного фенотипа с выработкой провоспалительных цитокинов, β-галоктозидазы, TGFβ и других факторов; блокировка митоза за счёт активной транскрипции генов *p16INK4A* и *p21CIP1*, участвующих в индукции клеточного старения. Предполагают, что такие клетки, названные сенесцентными, являются самостоятельным функциональным этапом цитогенеза в составе тканей, а не только переходной формой от активно функционирующего компонента дифферона к клеткам, погибающим путём программируемых видов клеточной гибели. Гистогенетическое значение сенесцентных клеток в физиологической и репаративной регенерации тканей, а также влияние на гистофизиологию требуют дальнейшего изучения. Фармакологическая элиминация сенесцентных клеток в составе тканей является активно разрабатываемым разделом антивозрастной терапии.

Ключевые слова: сенесцентные клетки; старение; гистогенез; возрастная гистология; возраст-ассоциированные заболевания.

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衰老细胞及其在组织发生结构中的位置

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摘要

老化或衰老（来自拉丁语。senex — 长者）是一个生物过程，包括身体各部分和系统在物质结构组织的不同层次上逐渐退化。 关于细胞衰老的复杂观点是当今描述整个身体衰老过程的主导概念。研究表明，在正在形成（产前组织生成）和最终定义的组织中的某些细胞经历了系列的形态功能变化：体积增大；染色质膜受损；形成特殊的异染色质区域；形成分泌表型，产生促炎细胞因子，β-半乳糖苷酶，TGFβ和其他因素；通过活性转录基因p16INK4A和p21CIP1阻止有丝分裂，这些基因参与诱导细胞老化。据推测，这种细胞被称为衰老细胞，是组织内细胞生成的一个独立功能阶段，而不仅仅是从一个活跃的功能成分到因程序性细胞死亡而死亡的细胞的过渡形式。衰老细胞在生理和修复性组织再生中的组织遗传学意义，以及对组织生理学的影响有待进一步研究。组织中衰老细胞的药物消除是抗衰老治疗的一个正在积极开发的部分。

关键词： 衰老细胞；老化；组织发生；年龄组织学；年龄相关疾病。

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CONCEPT OF SENESCENT CELLS

Aging, or senescence (from Latin *senex*—old man), is a biological process characterized by gradual degradation of organs and systems at various hierarchical levels of structural organization. According to Davydovsky (1966), aging is the gradual development of structural changes that are not caused by previous illnesses or injuries and increase the likelihood of death over time [1]. The concept of cellular aging as one of the mechanisms of "increasing entropy" in the body began to form in the second half of the 20th century. It is generally known that cellular aging is characterized by irreversible cessation of proliferation and the accumulation of some nonspecific morphofunctional changes. However, this process is non-stochastic, as it is accompanied by functional gene rearrangements, including the expression of negative regulators of the cell cycle [2]. Consequently, cellular aging is not based on "genetically determined repression of [*specific—author's note*] protein synthesis," but on changes in its profile. Thus, one cannot agree with the opinion of some authors [3] that cellular aging is synonymous with "age-related cell death." On the contrary, an important feature of senescent ("aged") cells (SCs) is their prolonged survival in tissue volume, which undoubtedly affects the structure and functional characteristics of the tissue. The induction of programmed cell death in SCs is the essence of a new pharmaceutical strategy of anti-aging therapy—the use of senolytic agents [4].

It is postulated that SCs, gradually accumulating in tissues, cause general aging of the body. This accompanies or leads to age-associated diseases. In addition, it has been shown that, due to their synthetic activity, SCs can participate in histogenetic processes (low-intensity inflammation, substitution), including the promotion of damaged tissue regeneration. At the same time, cellular aging with mitosis blockade is considered one of the forms of biological protection against malignant transformation [5].

An increase in the number of SCs has been observed both in the tissues of long-lived laboratory animals and in elderly people, patients with cancer undergoing chemotherapy, and in the development of age-related diseases [6]. In general, the analysis of scientific publications shows a relationship between cellular aging and chronological age. However, the strength of this relationship varies depending on the type of tissue (Table 1) and the SC marking method.

No universal biomarker that would be sufficient to verify cellular aging *in vivo* has been found yet [7]. In the studies, the most commonly used markers are senescence-associated beta-galactosidase (SA-β-gal), changes in the telomere length and telomerase activity, detection of double-strand DNA breaks, etc. [8–10]. At the same time, it has been shown that in some types of tissue, such as intestinal epithelium, prostate glandular epithelium, adipose tissue, and others, signs of cellular aging are not significantly related to chronological age [6].

SYSTEMIC STRUCTURAL ORGANIZATION OF HISTOGENESIS

Based on classic works by histologists in the second half of the 20th century, the concept of systemic structural organization of histogenesis was developed as the fundamental core of tissue theory [14]. There are several stages (factors, elementary processes) in the structure of

Table 1. Tissues demonstrated the presence of senescent cells

Tissue system	Tissue (type)	Marker of cellular aging and percentage of marker-positive cells, %	Age, months	Source
Epithelial cells	Small intestinal epithelium (mouse)	SA-β-gal: 0,3/3,3; p <0,05	2 and 24	[11]
Tissues of the internal environment	Adipose tissue (mouse)	SA-β-gal: 1,4/13,8; p <0,05	2 and 24	[11]
	Lymphoid tissue of the spleen (mouse)	SA-β-gal: 0,2/3,5; p <0,05	2 and 24	
	Lymphoid tissue of the lymph node (mouse)	SA-β-gal: 0,2/1,5; p <0,05	2 and 24	
	Epithelial tissue of the lung (mouse)	SA-β-gal: 5,9/6,7	2 and 24	
Muscle tissue and myoid cellular elements	Cardiomyocytes (mouse)	SA-β-gal: 4/60; p <0,001 p16: 10/38; p <0,001 p21: 11/42; p <0,001	3 and 18	[12]
Neural tissue	Hyppocampal pyramidal cells (rat)	SA-β-gal: 14,6/31,7/50,8; p <0,001	6, 18 and 24	[13]

Note: SA-β-gal, senescence-associated β-galactosidase; p16 and p21, cell cycle inhibitors; the proportion of cells positive for cell senescence markers is given as a percentage according to the age (e.g., 2 months/24 months).

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histogenesis, including proliferation, determination, migration, differentiation, specialization, growth, reproduction, integration, and death [15–17]. It seems appropriate to supplement the chain of logical events with the stage of cellular aging. This has already been partially reflected in scientific and educational works on histology [18].

Cellular aging is not mentioned in the scheme of structural organization of histogenesis proposed by Klishov (1984). According to the author, cell death is preceded by a special state known as necrobiosis (according to Virchow and Verworn), which usually means irreversible cellular changes. The term *paranecrosis* has been used for nearly nine decades to describe reversible (reactive) cellular changes [19]. Basically, the terms *necrobiosis* and *paranecrosis* are united by the tendency of cells to die and the uncertainty of the signs by which aging cells can be reliably detected in tissues. Knorre (1971) wrote about the phenomena preceding cell death in histogenesis: "...a distinction should be made between involution and subsequent cell death due to aging of the body as a whole; involution, cell death, and rejection as a result of wear and tear [*physiological cell regeneration—author's note*]; degradation and decay as a manifestation of far-reaching differentiation [*e.g., keratinization—author's note*]; pathological degeneration, which occurs only under special, rarely unfavorable conditions for the body or its part" (cited from Klishov [14]).

An important feature applicable to cellular aging is the detection of its signs among tissue cells as early as at the embryonic stage of development. This further illustrates that the chronological age of tissue and the body as a whole is not similar to their biological age, collectively and at the level of individual cells. It is worth noting, that cell death at the stages of embryonic histogenesis has long been recognized in the tissue theory [14, 20]. However, reliable identification of the stage of cellular aging in tissues of different ages has not yet been fully developed.

CONCEPT OF CELLULAR AGING

The term *cellular aging* was first proposed by Hayflick and Moorhead in 1961 while studying the causes of cell degeneration in primary cultures of human diploid fibroblasts [21], meaning that the morphofunctional characteristics associated with cellular aging were primarily a laboratory phenomenon. Cellular aging is characterized by the cessation of division due to the disruption of the structure of cellular organelles, epigenetic rearrangements, and changes in the cell secretome [21]. There are two types of cellular aging: replicative and stress-induced aging [4, 22].

Replicative aging is the result of multiple cycles of DNA replication during repeated cell divisions, which leads to telomere shortening. Many studies have shown a decrease in the proliferative potential of cells upon reaching the Hayflick limit, which, however, is not the same for different cell types and may vary depending on several factors, such as histogenetic origin, cultivation conditions, the presence and activity of telomerase, etc. The Hayflick limit typically ranges from 50 to 70 divisions. With each DNA replication, 50–200 base pairs of telomeres are lost because DNA polymerase cannot duplicate the entire molecule. The activation of the DNA damage response (DDR) results in the expression of cell cycle inhibitors *p16INK4A* and *p21CIP1*, which prohibit mitotic division [23–26].

In post-mitotic cells (G0), including most neurons and cardiomyocytes, cellular aging is characterized by DNA damage in telomeric regions and is independent of cell division or telomere length [27]. At the same time, a relationship was found between telomere shortening and the development of an aging-associated phenotype in neurons and astrocytes differentiated from induced human pluripotent stem cells [28].

A decrease in division rate during aging is accompanied by a gradual increase in size and change in the shape of most cells [29, 30]. SCs are characterized by shortened telomeric regions of chromosomes. However, the accumulating signs of aging correlate with an excess of a certain threshold of telomere shortening rather than with their gradual shortening as the number of replications increases. Aging cells have critically short telomeres, whereas cells with longer telomeres show no signs of aging [24].

An interesting natural model demonstrating the influence of telomere length on the development of age-related diseases is short telomere syndrome (STS), a spectrum of genetic disorders inherited in an autosomal dominant pattern and leading to telomere shortening. Due to its rarity and limited awareness among physicians, STS is likely to be underdiagnosed. This syndrome should be suspected if there are clinical signs such as premature graying of hair, idiopathic pulmonary fibrosis, cryptogenic liver cirrhosis, nodular regenerative hyperplasia of the liver, or a documented family history of these features [31].

It is believed that long telomere syndrome (LTS), on the contrary, is associated with an increased risk of malignancy formation rather than with signs of aging, including cellular aging. Mutations in telomerase and shelterin complex genes lead to an increase in the telomere length [26]. Telomerase is a unique enzyme that counteracts the shortening of telomeres during cell division by synthesizing end-terminal telomeric repeats, using its own transfer RNA as a template. An age-related decline in telomerase activity has been shown [32]. In most adult tissues, the expression of telomerase reverse transcriptase (TERT) is suppressed. In hematopoietic and other somatic stem cells, the level of telomerase remains low even when it is expressed, and does not compensate for the shortening of telomeres that occurs during aging. Somatic mutations in the proximal promoter of the *TERT* gene are currently considered to be a common non-coding mutation in cancer. For example, the vast majority of primary melanomas (67%–85%), glioblastomas (28%–84%), liposarcomas (74%–79%), and urothelial cancers (47%) contain *TERT* promoter

mutations. At the same time, critically shortened telomeres have also been identified in precancerous cells, which can be considered an initial protective mechanism that limits excessive proliferation of pathological cells.

Stress-induced cellular aging is associated with various factors that cause DNA damage, such as oxidative stress and mitochondrial dysfunction, activation of proto-oncogenes, and adverse environmental conditions, which partly links it to the phenomenon of nonspecific cellular (tissue) adaptation syndrome [33]. Damaging reactive oxygen species can also form due to exogenous factors such as UV radiation and chemicals from tobacco. These reactions reflect the DDR and activate the expression of *p21CIP1* and *p16INK4A*, leading to the signs of cellular aging [34].

MORPHOLOGICAL AND FUNCTIONAL CHARACTERISTICS OF SENESCENT CELLS

There are conflicting data on changes in the cell size during aging, both increase and decrease in the cell size have been described, which is most likely due to the analysis of different tissues. In some cases, there is atrophy of membrane structures, such as microvilli, intercellular contacts, etc. Intensification of mitochondrial leads to the formation of the "aging pigment," lipofuscin, which is accumulated in the cytoplasm. In aging cells, oxidative phosphorylation processes are less intensive and lead to a decrease in the amount of adenosine triphosphate (ATP) and NAD+ (the oxidized form of nicotinamide adenine dinucleotide). Thus, mitochondrial dysfunction is a characteristic feature of SCs and a consequence of the accumulation of such cells in tissues [35].

In SCs, autolysosomes gradually reduce their lytic activity, causing fat and pigment inclusions to accumulate in the cytoplasm. The cytoskeleton and karyoskeleton lose their locomotor functions, and the cytoplasm and nucleus become vacuolated [36]. The accumulation of autophagosomes on the trans side of the Golgi apparatus has been proposed to be considered as the formation of TOR-autophagy spatial coupling compartment (TASCC). Foci of heterochromatin associated with aging appear in the nucleus [37].

Changes in the nucleus and rearrangement of genetic material (senescence-associated heterochromatin foci, SAHF). A common feature of SCs is the enlargement and flattening of their nuclei (Table 2). In addition, the nuclei may be deformed, often fragmented, with nucleoli increasing in size and dispersing within the nucleus, leading to changes in the nuclear-cytoplasmic ratio [38]. These changes are associated with chromatin condensation, a response to DNA damage, and the appearance of senescence-associated heterochromatin foci (SAHF) [39]. SAHF appear as intensely stained areas within the nucleus that are rich in histone modifications responsible for suppressing the expression of the genes associated with proliferation, including key cell cycle regulators and DNA repair genes.

In vitro analysis of human fibroblasts undergoing replicative aging (in late passages) showed an increase in cell surface area along with a decrease in cell roundness, an increase in nuclear surface area, and an increase in the number of pseudopodia. The latter may be associated with the accumulation of cytoskeletal components, such as microtubules, microfilaments, intermediate filaments, and impaired intracellular transport and cell motility. It is worth mentioning that changes in cellular structures correlate more strongly with the donor age than with such indicators as ATP levels, secreted protein profiles, and responses to DNA damage [40]. An increase in the size of the nucleus and the cell itself during replicative aging is not universal. For example, in muscle fibers of young and elderly people, nuclear heteromorphism has been observed in elderly individuals, depending, among other things, on the type of muscle fiber [41, 42].

Changes in the nuclear size and shape are due to the remodeling of the structural elements of the nuclear

Table 2. Structural and functional characteristics of senescent cells

Structural characteristics	Functional characteristics
Nucleus: increase in size, change in shape, depletion of lamin B1, telomere shortening	Cell cycle arrest: expression of cyclin-dependent kinase inhibitor genes *p53/p21WAF1/CIP1*, *p16INK4a/pRB* SAHF Decrease in the DDR telomerase activity (γH2AX)
Cytoskeleton: reduction in the number of microtubules	Decreased intracellular transport intensity
Biosynthesis organelles: expansion of the endoplasmic reticulum Mitochondria: vacuolization, cristae damage, decrease in size Increase in the number of lysosomes	SASP: IL-1, IL-2, IL-6; chemokines MCP-1, CCL2,3 ; growth factors TGFβ, PAI-1 Increase in the SA-β-gal activity SCAP: *ATG5, ATG7, BECN1*

Note: SASP , senescence-associated secretory phenotype; DDR, DNA damage response; SA-β-gal, senescence-associated β-galactosidase; SAHF, senescence-associated heterochromatin foci; SCAP, senescent cell anti-apoptotic pathways.

cytoskeleton (nucleoskeleton). The inner nuclear membrane is lined with the nuclear lamina, which consists of a network of proteins involved in maintaining chromatin configuration. Diseases caused by the dysfunction of lamins (the main proteins that form the nuclear lamina), Werner syndrome and Hutchinson–Gilford progeria syndrome, are characterized by premature aging in children and adults, respectively. Most patients with Hutchinson–Gilford progeria syndrome have the G608G (GGC > GGT) mutation in exon 11 of the lamin A gene, and the fibroblasts of these patients are characterized by fragmented nuclei and disorganization of centromeres and lamins A and B [43]. Some studies show that depletion of lamin B precedes the appearance of senescence-associated heterochromatin foci [44]. Lamins regulate gene expression and inhibit transposons, in particular LINE retrotransposons and LTR elements, whose activity increases with cellular aging and is one of the causes of genome instability, including telomere shortening, accumulation of DNA damage, disruption of DNA repair mechanisms, and epigenetic changes. Consequently, disruption of lamin regulation associated with inactivating mutations in the respective genes or with a decrease in their expression is one of the factors contributing to cellular aging [45, 46].

Histones are lost during replicative and stress-induced aging of mammalian cells. Depending on the cell type, either all or certain types of histones may be sensitive to replicative aging. It has been shown that the content of histones H3 and H4 in dermal fibroblasts decreases by 43% and 47%, respectively, while myosatellites of old mice lose histones H1, H2B, H3, and H4. The histone loss has also been observed in T lymphocytes and in retinal pigment epithelial cells. Moreover, age-related histone loss occurs in both actively proliferating and postmitotic cells. As nucleosome destabilization significantly increases chromatin accessibility, SCs are characterized by more active transcription and genome instability [47, 48].

Changes in the cytoskeleton. Aging processes have the greatest impact on the cytoskeleton of the cells, whose functions are associated with high mobility or complex structural organization [49, 50].

The reorganization of microtubules in the axons of the human and primate brain during aging is due to the alterations in post-translational modifications of tubulin isoforms and other proteins associated with microtubules. In senescent microglia, the balance of these proteins is disrupted, leading to difficulties in cytoskeletal assembly, reduced microglia motility, and the formation of neurofibrillary tangles [51]. The disorganization of microtubules during aging leads to axonal thinning and the formation of axonal swellings [52]. In neurodegenerative diseases (Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis, frontotemporal dementia), there is a marked breakdown of axonal microtubule bundles [53, 54].

The impaired phagocytic activity of senescent macrophages has been found to be associated with changes in the cytoskeleton. Alveolar macrophages in aging mice (old animals often serve as models to study SCs) are characterized by reduced expression of mRNA for the GTP-binding protein Rac1, which is necessary for the activation of the Arp2/3 complex (Actin-Related Proteins 2 and 3), which, in turn, leads to weakened F-actin polymerization [55].

Aging cells secrete a complex of pro-inflammatory cytokines and enzymes, in particular proteases, which are collectively referred to as the **senescence-associated secretory phenotype (SASP)**. SASP helps maintain low-intensity inflammation in tissues [56].

SENESCENT CELLS IN TISSUE STRUCTURE

The amount of collagen in the tissues of an aging body varies from 1% to 20% depending on the type of tissue, age, and many other factors [11, 57]. The presence of senescent cells has been demonstrated in many tissues and structures of the embryo, indicating that aging is a programmed component of normal embryonic development and plays an important role in histogenesis and organogenesis [58]. SA-β-gal-positive cells were detected in the mesonephros, the lining of the endolymphatic sac of the inner ear, and in the apical ectodermal ridge of the limb buds. In murine embryos (E11.5–E15.5), a statistically significant negative correlation was demonstrated between the presence of SA-β-gal-positive cells and the expression of the Ki67 proliferation marker [59]. In the area of apical ectodermal ridge of murine and chicken embryos, mature F4/80-positive macrophages surrounding senescent cells were identified [60]. It is believed that programmed cell aging is accompanied by cell removal and subsequent tissue remodeling, with cellular aging itself acting as a control point that limits pathological proliferation and is necessary for the regulation of embryogenesis [61].

Cellular aging serves as both an important mechanism of normal embryogenesis and a regulator of tissue regeneration processes. Several studies have demonstrated the presence of SCs in the regeneration area after limb amputation in salamanders [62] and fin amputation in zebrafish (*Danio rerio*) [63]. A study of heart regeneration in newborn mice showed the presence of senescent cells (SA-β-gal- and SASP-positive) on days 3, 7, and 14 after apical resection, as well as the absence of SCs on day 21, i.e., in a fully regenerated heart. At the same time, the use of the senolytic agent ABT263[1] enhanced substitution and the formation of fibrous scars [64]. An experimental study on mice has

[1] The drug is not authorized in the Russian Federation.

demonstrated that the application of the senolytic agent ABT263 reduces the number of SCs in the area of skeletal muscle damage, leading to impaired regeneration [65]. In contrast, elimination of SCs using dasatinib and quercetin enhanced muscle regeneration after injury [66].

The data on the functional activity of SCs available to date do not allow drawing definitive conclusions about their involvement in histophysiological processes and its consequences [67]. The contradictory nature of the obtained data led to the emergence of the concept of senescent cell heterogeneity, which distinguishes the so-called "harmful" and "beneficial" variants of SCs, exerting directly opposite effects on regenerative histogenesis and low-intensity inflammation [68, 69]. In addition, the concept of physiological (transient, in the authors' terms) and aberrant cellular aging has been formed. According to the authors, in the first case, under the influence of damaging factors, SCs can accumulate in tissues, including during chronological aging, but they are effectively eliminated by immune system cells. In contrast, in aberrant aging, senescent cells suppress the activity of the microenvironment through SASP, thereby contributing to the formation of a pathological tissue development pattern [70].

CONCLUSION: THE ROLE OF SENESCENT CELLS IN HISTOGENESIS

Thus, over the past three decades, reproducible data have been obtained on stereotypical nonspecific morphofunctional changes in the cells of various histogenetic origins, including information on structural rearrangements of cellular compartments and changes in gene activity, including those that ensure the synthesis of proinflammatory cytokines and certain growth factors. Apparently, these characteristics predetermine manifestations of low-intensity inflammation in tissues and hyperplasia of the connective tissue stroma, increasing with chronological age. Moreover, the described cellular changes are not necessarily a stage preceding some type of cell death. However, the latter requires further investigation, at least from the point of view of micro- and macroautophagy development.

The histophysiological effect of the synthetic activity of SCs is not limited to the features listed above, but also includes a direct impact on the cellular regeneration of specialized tissues, as demonstrated in several experimental studies. The summarized data allows us to suggest that cellular aging should be viewed as a distinct stage (factor, elementary process) of histogenesis, not identical to the intermediate state between "life and death" (paranecrosis, necrobiosis; Fig. 1).

The morphofunctional characteristics of SCs can be identified in comprehensive histological, histochemical, immunohistochemical, molecular genetics, and ultrastructural studies. SCs have been detected (visualized) in some tissues of the body (Table 1). This allows us to conclude that cellular

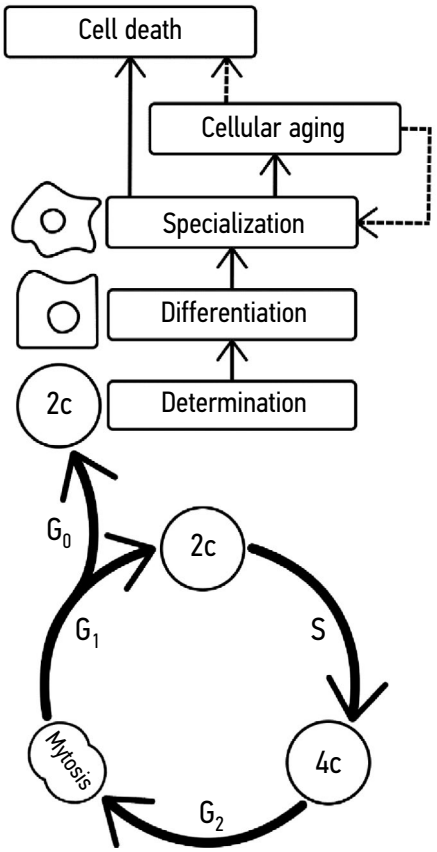

Fig. 1. Structural scheme of histogenesis made by the authors.

senescence should currently be considered not only and not so much as an *in vitro* phenomenon associated with the induction of replicative or stress-induced aging in the absence of distant and contact interaction with the cells of the integrative systems, including the immune, endocrine, and nervous systems.

ADDITIONAL INFORMATION

Author contributions: All authors approved the version of the manuscript to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The primary contributions were distributed as follows. R.V. Deev, K.V. Kotenko: conceptualization, methodology, R.V. Deev, Yu.V. Markina, T.V. Kirichenko: investigation, resources, R.V. Deev, Yu.V. Markina, T.V. Kirichenko, I.V. Zhivodernikov, A.M. Markin, I.I. Yeremin: writing—original draft, writing—review & editing.

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REFERENCES | СПИСОК ЛИТЕРАТУРЫ

1. Anichkov NM, Kvetnoi IM. The role of I.V. Davydovski in the development of gerontology. *Advances in Gerontology*. 2002;9(3):257. (In Russ.) EDN: YCTKNV

2. DiLoreto R, Murphy CT. The cell biology of aging. *Mol Biol Cell*. 2015;26(25):4524–4531. doi: 10.1091/mbc.E14-06-1084 EDN: WRGIFB

3. Lushnikov EF. *Death of the human being and its organs, tissues and cells. Modern ideas*. Obninsk; 2024. (In Russ.)

4. Kirichenko TV, Markina YuV, Markin AM, et al. Senescent cells: a therapeutic target in correction of aging. *Regenerative Biotechnologies, Preventive, Digital and Predictive Medicine*. 2024;1(3):53–63. (In Russ.) doi: 10.17116/rbpdpm2024103153 EDN: FHIPKL

5. Choi EL, Taheri N, Chandra A, Hayashi Y. Cellular Senescence, Inflammation, and Cancer in the Gastrointestinal Tract. *Int J Mol Sci*. 2023;24(12):9810. doi: 10.3390/ijms24129810 EDN: FYBNLD

6. Tuttle CSL, Waaijer MEC, Slee-Valentijn MS, et al. Cellular senescence and chronological age in various human tissues: A systematic review and meta-analysis. *Aging Cell*. 2020;19(2):e13083. doi: 10.1111/acel.13083 EDN: DEJOAZ

7. Ogrodnik M, Carlos Acosta J, Adams PD, et al. Guidelines for minimal information on cellular senescence experimentation in vivo. *Cell*. 2024;187(16):4150–4175. doi: 10.1016/j.cell.2024.05.059 EDN: FCJVFN

8. Morgunova GV, Kolesnikov AV, Klebanov AA, Khokhlov AN. Senescence-associated β-galactosidase-a biomarker of aging, DNA damage, or cell proliferation restriction? *Moscow University Biological Sciences Bulletin*. 2015;(4):15–18. (In Russ.) EDN: UXOJVH

9. Anderson R, Lagnado A, Maggiorani D, et al. Length-independent telomere damage drives post-mitotic cardiomyocyte senescence. *EMBO J*. 2019;38(5):e100492. doi: 10.15252/EMBJ.2018100492

10. Bernardes de Jesus B, Blasco MA. Assessing cell and organ senescence biomarkers. *Circ Res*. 2012111(1):97–109. doi: 10.1161/CIRCRESAHA.111.247866 EDN: JRAEBL

11. Biran A, Zada L, Abou Karam P, et al. Quantitative identification of senescent cells in aging and disease. *Aging Cell*. 2017;16(4): 661–671. doi: 10.1111/acel.12592

12. Li G, Zhang D, Wang S, et al. Protective Role of Taraxasterol against Cardiovascular Aging and Aging-Induced Desensitization of Insulin Signaling. *Front Biosci (Landmark Ed)*. 2022;27(11):311. doi: 10.31083/j.fbl2711311 EDN: EMDIYZ

13. Geng YQ, Guan JT, Xu XH, Fu YC. Senescence-associated beta-galactosidase activity expression in aging hippocampal neurons. *Biochem Biophys Res Commun*. 2010;396(4):866–869. doi: 10.1016/j.bbrc.2010.05.011 EDN: NWJHYT

14. Klishov AA. *Histogenesis and tissue regeneration*. Leningrad: Meditsina; 1984. (In Russ.)

15. Schelkunov SL. *The Principles of cellular differentiation*. Moscow: Meditsina; 1977. (In Russ.)

16. Danilov RK, Borovaia TG, Klochkov ND. Experimental and histological analysis of histogenesis and tissue regeneration (some results of the 20th century and perspectives on further research). *Morphology*. 2000;117(4):7–16. (In Russ.) EDN: MQKGEV

17. Danilov RK. General principles of cellular organisation, development and classification of tissues. In: Danilov RK, editor. *Manual of histology*. 2nd ed. Saint Petersburg: SpetsLit; 2011. P: 98–123. (In Russ.)

18. Myadelets OD. *Fundamentals of human age-related histology: textbook*. Vitebsk: Vitebskiy gosudarstvennyy ordena Druzhby narodov meditsinskiy universitet, 2024. (In Russ.) ISBN: 978-985-580-197-0 EDN: DAJSIE

19. Nasonov DN, Aleksandrov VYa. *Response of living matter to external influences*. Moscow, Leningrad: Izd-vo Akad. nauk SSSR; 1940. (In Russ.)

20. Deev RV, Bilyalov AI, Zhampeisov TM. Modern ideas about cell death. *Genes & Cells*. 2018;13(1):6–19. (In Russ.) doi: 10.23868/201805001 EDN: YNQDVJ

21. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res*. 1961;25:585–621. doi: 10.1016/0014-4827(61)90192-6

22. Gorgoulis V, Adams PD, Alimonti A, et al. Cellular senescence: Defining a path forward. *Cell*. 2019;179(4): 813–827. doi: 10.1016/j.cell.2019.10.005 EDN: PGJUED

23. Jiang J, Wang Y, Sušac L, et al. Structure of telomerase with telomeric DNA. *Cell*. 2018;173(5):1179–1190.e13. doi: 10.1016/j.cell.2018.04.038 EDN: VFVENU

24. Nassrally MS, Lau A, Wise K, et al. Cell cycle arrest in replicative senescence is not an immediate consequence of telomere dysfunction. *Mech Ageing Dev*. 2019;179:11–22. doi: 10.1016/j.mad.2019.01.009

25. Afifi MM, Crncec A, Cornwell JA, et al. Irreversible cell cycle exit associated with senescence is mediated by constitutive MYC degradation. *Cell Rep*. 2023;42(9):113079. doi: 10.1016/j.celrep.2023.113079 EDN: IHGSVZ

26. Mylonas A, O'Loghlen A. Cellular senescence and ageing: Mechanisms and interventions. *Front Aging*. 2022;3:866718. doi: 10.3389/fragi.2022.866718 EDN: BQSPHC

27. Anderson R, Lagnado A, Maggiorani D, et al. Length-independent telomere damage drives post-mitotic cardiomyocyte senescence. *EMBO J*. 2019;38(5):e100492. doi: 10.15252/embj.2018100492

28. Harley J, Santosa MM, Ng CY, et al. Telomere shortening induces aging-associated phenotypes in hiPSC-derived neurons and astrocytes. *Biogerontology*. 2024;25(2):341–360. doi: 10.1007/s10522-023-10076-5 EDN: BEGUSA
29. Lanz MC, Zatulovskiy E, Swaffer MP, et al. Increasing cell size remodels the proteome and promotes senescence. *Mol Cell*. 2022;82(17):3255–3269.e8. doi: 10.1016/j.molcel.2022.07.017 EDN: ZKTAKE
30. Neurohr GE, Terry RL, Lengefeld J, et al. Excessive cell growth causes cytoplasm dilution and contributes to senescence. *Cell*. 2019;176(5):1083–1097.e18. doi: 10.1016/j.cell.2019.01.018 EDN: BRJMLC
31. Baird A, Gomes M, Souza CA, et al. Short Telomere Syndrome presenting with pulmonary fibrosis, liver cirrhosis and hepatopulmonary syndrome: a case report. *BMC Pulm Med*. 2023;23(1):114. doi: 10.1186/s12890-023-02378-8 EDN: DFUVPH
32. Spivak IM, Mikhelson VM, Spivak DL. Telomere length, telomerase activity, stress and aging. *Advances in Gerontology*. 2015;28(3): 441–448. (In Russ.) EDN: UYLYSH
33. Braun AD, Mozhenok TP. *Non-specific cellular system adaptation*. Leningrad: Nauka; 1987. (In Russ.)
34. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021;22(2):75–95. doi: 10.1038/s41580-020-00314-w EDN: HMSHWJ
35. Chini CCS, Cordeiro HS, Tran NLK, Chini EN. NAD metabolism: Role in senescence regulation and aging. *Aging Cell*. 2024;23(1):e13920. doi: 10.1111/acel.13920
36. Tominaga K. The emerging role of senescent cells in tissue homeostasis and pathophysiology. *Pathobiol Aging Age Relat Dis*. 2015;5:27743. doi: 10.3402/pba.v5.27743
37. Narita M, Young AR, Arakawa S et al. Spatial coupling of mTOR and autophagy augments secretory phenotypes. *Science*. 2011;332(6032):966–970. doi: 10.1126/science.1205407
38. Belhadj J, Surina S, Hengstschläger M, Lomakin AJ. Form follows function: Nuclear morphology as a quantifiable predictor of cellular senescence. *Aging Cell*. 2023;22(12):e14012. doi: 10.1111/acel.14012 EDN: BSLBWC
39. Gao E, Sun X, Thorne RF, et al. NIPSNAP1 directs dual mechanisms to restrain senescence in cancer cells. *J Transl Med*. 2023;21(1):401. doi: 10.1186/s12967-023-04232-1 EDN: MWRDBK
40. Welter EM, Benavides S, Archer TK, et al. Machine learning-based morphological quantification of replicative senescence in human fibroblasts. *Geroscience*. 2024;46(2):2425–2439. doi: 10.1007/s11357-023-01007-w EDN: IMNPWZ
41. Cristea A, Qaisar R, Edlund PK, et al. Effects of aging and gender on the spatial organization of nuclei in single human skeletal muscle cells. *Aging Cell*. 2010;9(5):685–697. doi: 10.1111/j.1474-9726.2010.00594.x EDN: NZOSIB
42. Cisterna B, Malatesta M. Molecular and structural alterations of skeletal muscle tissue nuclei during aging. *Int J Mol Sci*. 2024;25(3):1833. doi: 10.3390/ijms25031833 EDN: CDMPIW
43. Taimen P, Pfleghaar K, Shimi T, et al. A progeria mutation reveals functions for lamin A in nuclear assembly, architecture, and chromosome organization. *Proc Natl Acad Sci U S A*. 2009;106(49):20788–20793. doi: 10.1073/pnas.0911895106
44. Sadaie M, Salama R, Carroll T, et al. Redistribution of the Lamin B1 genomic binding profile affects rearrangement of heterochromatic domains and SAHF formation during senescence. *Genes Dev*. 2013;27(16):1800–1808. doi: 10.1101/gad.217281.113 EDN: RMWXUF
45. Mustafin RN, Khusnutdinova EK. The relationship of lamins with epigenetic factors during aging. *Vavilov Journal of Genetics and Breeding*. 2022;26(1):40–49. doi: 10.18699/VJGB-22-06 EDN: CUVKWK
46. Kristiani L, Kim M, Kim Y. Role of the nuclear lamina in age-associated nuclear reorganization and inflammation. *Cells*. 2020;9(3):718. doi: 10.3390/cells9030718 EDN: UFHLED
47. Soto-Palma C, Niedernhofer LJ, Faulk CD, Dong X. Epigenetics, DNA damage, and aging. *J Clin Invest*. 2022;132(16):e158446. doi: 10.1172/JCI158446 EDN: QPZPGS
48. López-Gil L, Pascual-Ahuir A, Proft M. Genomic instability and epigenetic changes during aging. *Int J Mol Sci*. 2023;24(18):14279. doi: 10.3390/ijms241814279 EDN: KBUINW
49. Pradeau-Phélut L, Etienne-Manneville S. Cytoskeletal crosstalk: A focus on intermediate filaments. *Curr Opin Cell Biol*. 2024;87:102325. doi: 10.1016/j.ceb.2024.102325 EDN: HXJFIA
50. Schmidt CJ, Stehbens SJ. Microtubule control of migration: Coordination in confinement. *Curr Opin Cell Biol*. 2024;86:102289. doi: 10.1016/j.ceb.2023.102289 EDN: TRHOXY
51. Socodato R, Relvas JB. A cytoskeleton symphony: Actin and microtubules in microglia dynamics and aging. *Prog Neurobiol*. 2024;234:102586. doi: 10.1016/j.pneurobio.2024.102586 EDN: XHPWGM
52. Okenve-Ramos P, Gosling R, Chojnowska-Monga M, et al. Neuronal ageing is promoted by the decay of the microtubule cytoskeleton. *PLoS Biol*. 2024;22(3):e3002504. doi: 10.1371/journal.pbio.3002504 EDN: AVYDQG
53. Kounakis K, Tavernarakis N. The cytoskeleton as a modulator of aging and neurodegeneration. *Adv Exp Med Biol*. 2019;1178:227–245. doi: 10.1007/978-3-030-25650-0_12 EDN: CLUGNY
54. Sferra A, Nicita F, Bertini E. Microtubule dysfunction: A common feature of neurodegenerative diseases. *Int J Mol Sci*. 2020;21(19):7354. doi: 10.3390/ijms21197354 EDN: GWEPNN
55. Li Z, Jiao Y, Fan EK, et al. Aging-impaired filamentous actin polymerization signaling reduces alveolar macrophage phagocytosis of bacteria. *J Immunol*. 2017;199(9):3176–3186. doi: 10.4049/jimmunol.1700140
56. Kuehnemann C, Wiley CD. Senescent cells at the crossroads of aging, disease, and tissue homeostasis. *Aging Cell*. 2024;23(1):e13988. doi: 10.1111/acel.13988 EDN: AMCLZI
57. Olan I, Handa T, Narita M. Beyond SAHF: An integrative view of chromatin compartmentalization during senescence. *Curr Opin Cell Biol*. 2023;83:102206. doi: 10.1016/j.ceb.2023.102206 EDN: XLAPMS
58. Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. *Nat Rev Mol Cell Biol*. 2014;15(7):482–496. doi: 10.1038/nrm3823 EDN: USWTWN
59. Muñoz-Espín D, Cañamero M, Maraver A, et al. Programmed cell senescence during mammalian embryonic development. *Cell*. 2013;155(5):1104–1118. doi: 10.1016/j.cell.2013.10.019
60. Storer M, Mas A, Robert-Moreno A et al. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. *Cell*. 2013;155(5):1119–1130. doi: 10.1016/j.cell.2013.10.041
61. Calcinotto A, Kohli J, Zagato E, et al. Cellular Senescence: Aging, Cancer, and Injury. *Physiol Rev*. 2019;99(2):1047–1078. doi: 10.1152/physrev.00020.2018 EDN: XAESJN

62. Yun MH, Davaapil H, Brockes JP. Recurrent turnover of senescent cells during regeneration of a complex structure. *Elife*. 2015;4:e05505. doi: 10.7554/eLife.05505
63. Da Silva-Álvarez S, Guerra-Varela J, Sobrido-Cameán D, et al. Cell senescence contributes to tissue regeneration in zebrafish. *Aging Cell*. 2020;19(1):e13052. doi: 10.1111/acel.13052
64. Feng T, Meng J, Kou S, et al. CCN1-induced cellular senescence promotes heart regeneration. *Circulation*. 2019;139(21):2495–2498. doi: 10.1161/CIRCULATIONAHA.119.039530
65. Young LV, Wakelin G, Cameron AWR, et al. Muscle injury induces a transient senescence-like state that is required for myofiber growth during muscle regeneration. *FASEB J*. 2022;36(11):e22587. doi: 10.1096/fj.202200289RR EDN: EUGJGI
66. Moiseeva V, Cisneros A, Sica V, et al. Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration. *Nature*. 2023;613(7942):169–178. doi: 10.1038/s41586-022-05535-x EDN: ZQIZZC
67. de Magalhães JP. Cellular senescence in normal physiology. *Science*. 2024;384(6702):1300–1301. doi: 10.1126/science.adj7050 EDN: DMDQIN
68. Tripathi U, Misra A, Tchkonia T, Kirkland JL. Impact of senescent cell subtypes on tissue dysfunction and repair: Importance and research questions. *Mech Ageing Dev*. 2021;198:111548 doi: 10.1016/j.mad.2021.111548 EDN: EVIZCP
69. Shvedova M, Samdavid Thanapaul RJR, Thompson EL, et al. Cellular senescence in aging, tissue repair, and regeneration. *Plast Reconstr Surg*. 2022;150:4S–11S. doi: 10.1097/PRS.0000000000009667 EDN: NXWUCH
70. Rhinn M, Ritschka B, Keyes WM. Cellular senescence in development, regeneration and disease. *Development*. 2019;146(20):dev151837. doi: 10.1242/dev.151837 EDN: XMSQIZ

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