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CELLULAR SENESCENCE AS A QUALITY PARAMETER IN CHRONOLOGICAL AGING

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ABSTRACT

Chronological aging and its difference with biological aging have been the subject of study for many years, trying to define within biological aging the causes or pathways by which this process of homeostatic deterioration occurs. Until the beginning of this year, 13 "Hallmarks of aging" have been defined, which describe the aging process from a molecular, cellular and systemic point of view, which are DNA instability, telomere

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attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, disabled macroautophagy, chronic inflammation, and dysbiosis. When conducting research on each of them, our attention was drawn to the close relationship between all of them and cellular senescence as a result of most of these processes. Cellular senescence refers to an irreversible form of long-term arrest of the cell cycle, which causes a loss of the ability to participate in tissue repair, in addition to damage caused through the secretion of senescence-associated secretory phenotype (SASP), which is closely linked to all known processes of biological aging. In this article we describe what cellular senescence is, what are the different processes or "Hallmarks" of aging currently defined, and their close relationship with cellular senescence. In addition, we took different approach to senescence to use it as a quality metric in chronological aging, instead of using it to define a biological age as it has been approached in the past.

KEYWORDS: Cellular senescence, Biomarkers, Cellular aging, Inmunosenescence.

BACKGROUND

Aging can be defined as a proliferative, time-related deterioration of the

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physiological processes of the organism that maintain its survival and fertility (1). However, the observation that individuals do not age at the same pace led to the definition of biological aging, also called functional or physiological aging. Whereas chronological aging refers only to the passage of time, biological aging relates to decline in function (2).

While chronological age is arguably the strongest risk factor for aging-related death and disease, it is important to distinguish chronological time from biological aging. Individuals of the same chronological age may exhibit greatly different susceptibilities to age- related diseases and death, which is likely reflective of differences in their underlying biological aging processes (3). The chronological age is only the evaluation indicators of time scale in the aging process. Therefore, biological age can be more representative of the true degree of aging than chronological age, which provides a quantitative standard for individualized aging (4).

In 2013, Carlos López-Otín et al. published the first edition of the 9 "Hallmarks of aging" focused on biological aging at the molecular, cellular and systemic level: Genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (5). Recently, in January 2023, a new update was published that includes 3 new hallmarks: disabled macroautophagy, chronic inflammation, and dysbiosis (6). The distinction among “hallmarks” is intrinsically diffuse, since they interact and are not independent from each other. The interdependence of aging hallmarks means that the experimental accentuation or attenuation of one specific hallmark usually affects other hallmarks as well. However, one deserves special attention

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as a key factor in this complex process, due to its notable relationship with the other hallmarks, not during their processes but because of them: cellular senescence (7).

MATERIALS AND METHODS

This study, according to the classification given by Hernández, Fernández and Baptista (8), had an exploratory scope with an explanatory design. The development of this study was based on the extension guide of the PRISMA (Preferred Reporting Items for Systematic Reviews and Metananalyses) declaration, PRISMS-ScR (9) published in 2018 and with the guide of the Joanna Briggs Institute for conducting systematic scoping reviews. (10).

1.2 Search strategy

The search was carried out independently, the last search was carried out until March 2023. The search strategy was focused on the last 10 years, using the terms in English for the Pubmed/Medline/NCBI and Scopus databases. The keywords CELLULAR SENESCENCE, HALLMARKS OF AGING, AGING AND SENESCENCE, BIOLOGICAL AGING AND SENESCENT CELLS were used for the search.

2.3 Inclusion and Exclusion Criteria

In the inclusion criteria, the following were accepted: 1. Articles that evaluate cellular senescence, 2. In vitro and in vivo studies and documentary reviews, 3. Articles that relate cellular senescence with aging. The exclusion criteria were: duplicate articles, irrelevant studies, manuscripts, letters to the editor, specialist comments, and unreviewed articles.

2.4 Data Extraction

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The articles found were divided according to their object of study, classifying them into: cellular aging, biological aging, cellular senescence, and hallmarks of aging.

RESULTS

3.1 Study selection

The search identified a total of 11,102 articles, repeated articles were eliminated and articles that included at least 3 of the keywords used were separated, giving a total of 618 results which were analyzed by their titles and abstracts. Considering the inclusion and exclusion criteria, 61 articles were chosen. Table 1 shows the most relevant studies due to their methodological rigor. It is considered that the results and conclusions represent an important contribution to the development of the topic.

Table 1 Studies with the most relevance

AUTHOR	STUDY DESIGN	OBJECTIVE	SAMPLE SIZE	MAIN CONTRIBUTION
Lopez-Otın C y Cols (6)	Review article	To Describe the 12 hallmarks of aging, their relationship to each other, and why 3 new hallmarks were added.	300 articles	Describes each of the hallmarks of aging to date
Faget, D.V y Cols (16)	Review article	To Describe the impact of a senescent cell depending on its cell and tissue of origin	165 articles	Highlights the side effect of SASP and how it changes depending on the secretory cell of origin.
Fafian-Labora y Cols (44)	Review article	To Review the different pathways of intercellular communication in the context of senescence and aging	90 articles	It demonstrates SASP as the main pathway of communication between senescent cells and as the first cause of its

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				pathological effect.
Jeon, O. H. y Cols (58)	Experimental *In vitro*	To Examine the relationship between senescent chondrocytes and osteoarthritis	12 Experiments were performed in samples of 40 rats each	The elimination of senescent cells allows a more accelerated recovery of the cartilage
Levi, N y Cols (45)	Review article	To Relate the function of the extracellular matrix components with the state of senescence	85 articles	It allowed to relate most of the hallmarks of aging with senescence due to changes in the extracellular matrix
Robbins, P.D y Cols (60)	Review article	To Review the evidence linking cellular senescence to aging and disease	97 articles	Showed senescence as one of the main causes of aging for a therapeutic approach
Nik-Zainal, S., and Hall, B.A. (19)	Review article	To show that the integrity of cell function has a greater influence than genomic stability	14 articles	Showed that sustained cell function has greater survival benefit than genomic preservation

CELLULAR SENESCENCE

Senescence (from the Latin “senex” which means to age) is an irreversible form of long-term arrest of the cell cycle, caused by excessive intra- or extracellular damage or stress (11). Hayflick and Moorhead in 1961 argued that tissues age because senescent, or non-dividing cells (SNC) lose the ability to participate in repairing the tissue itself. What could not be appreciated at the time was that these cells are also harmful for an entirely different reason. In addition, to not being able to contribute to tissue repair through proliferation, the SNCs disrupt normal tissue function by secreting factors called senescence-associated factor (SASP) phenotypes, which secrete

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proinflammatory substances, induce remodeling of the extracellular matrix, stimulate apoptosis in other unwanted cell types, induce fibrosis and inhibit stem cell function (12,13,14). The SNC that accumulate over time cause active damage to the tissues in which they are found and are directly linked to characteristics of natural aging (15).

Therefore, SASP explains the pathogenic role of the SNC through its conflicting consequences on the cellular microenvironment: (1) it recruits and activates cells of the immune system through the secretion of chemokines and cytokines; (2) suppresses the immune system through the secretion of TGF-β; (3) stimulates fibroblast activation and collagen disposition via pro-fibrotic factors (TGF-β, IL-11, and PAI1); (4) remodels the extracellular matrix through the secretion of metalloproteases; (5) stimulates the activation and proliferation of progenitor cells through the secretion of growth factors (EGF and PDGF); (6) stimulates paracrine senescence in neighboring cells (TGF-β, TNF-α, IL-8) (16).

Now we are going to describe the relationship between SNCs and the different hallmarks of aging, either directly or through SASP

GENOMIC INSTABILITY

This refers to the accumulation of genetic damage throughout one's lifespan, due to a multitude of DNA alterations like mutations, indels and chromosomal rearrangements. Attributed to endogenous (Reactive Oxygen Species -ROS-, DNA replication errors, among others) and exogenous (environment, iatrogenic) agents, genomic instability often accompanies biological aging, while its artificial induction can frequently lead to an accelerated aging phenotype (17). All of these DNA alterations can affect essential genes and transcriptional

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pathways, resulting in dysfunctional cells that compromise tissue and organismal homeostasis. This is relevant when DNA damage impacts stem cells, affecting their tissue renewal function or leading to their exhaustion (18).

The accumulation of DNA mutations during the life cycle is probably tolerated due to the high energy cost necessary to repair all the genomic damage, consequently the cells favor survival over genomic integrity, entering a state of senescence (19).

TELOMERE ATTRITION

Loss of noncoding DNA base pairs located at the ends of chromosomes (telomeres) contributes to aging and age-linked diseases. DNA replication polymerases are unable to complete the copies of telomere regions in the DNA, thus, after several rounds of cell divisions, the telomeres undergo a substantial shortening (between 50 and 200 bp for each mitotic division), that induces genomic instability and finally leads to either apoptosis or cell senescence (20).

Telomere shortening is one of the hallmarks of aging on which more information is currently available and that has been associated with inducing cellular senescence (21).

EPIGENETIC ALTERATIONS

A large variety of epigenetic changes that contribute to aging include alterations in DNA methylation patterns, abnormal post-translational modification of histones, aberrant chromatin remodeling, and deregulated function of non-coding RNA. These regulatory and often reversible changes have impact on gene expression and other cellular processes resulting in the development and progression of various diseases (22). Although it is still not clear how most of these alterations lead to senescence, it’s

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been possible to identify an attenuation in the effects of the SNC by improving the abnormalities in chromatin remodeling and histone modifications (23). Similarly, a reactivation of retrotransposons has been observed in the increased presence of SNC that generate deleterious epigenetic changes, and an acceleration in the aging of laboratory rats (24,25).

LOSS OF PROTEOSTASIS

A highly regulated network of proteins comprising of molecular chaperones, proteolytic systems, and regulators is crucial to maintain a stable proteome or protein homeostasis (proteostasis) (26). Aging, age-related pathologies and certain neurodegenerative diseases show a deterioration in proteostasis with accumulation of intracellular damage, which as a consequence leads to the appearance of the SNC (27).

DISABLED MACROAUTOPHAGY

Macroautophagy involves the sequestration of cytoplasmic material in two-membrane vesicles, the autophagosomes, which later fuse with lysosomes for the digestion of luminal content. Autophagy is not only involved in proteostasis, but also affects non-protein macromolecules and whole organelles, as well as invading pathogens. An age-related decline in autophagy constitutes one of the most important mechanisms of reduced organelle turnover (28). There is currently no information linking this hallmark to SNC induction; however, its presence is related to a suppression of apoptosis, which leads to a greater SASP secretion, consequently a higher rate of senescence, and sometimes the emergence of cancer due to the consequent immunosenescence (29,30,31,32,33).

DEREGULATED NUTRIENT-SENSING

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Nutrient availability and sensing are major regulators of cell-signaling pathways that take cues from environmental stimuli and intracellular activity to maintain energy homeostasis within a cell. These pathways determine cellular energy levels, communicate and coordinate with hormonal and nutrient signaling cascades to induce a positive feedback loop whereby an optimal level is achieved. However, with aging there is a decline in the cell's ability to maintain metabolic homeostasis due to failure and deterioration of these pathways, contributing to the organismal aging phenotype (34).

Some of the most affected pathways are the Somatotropic Axis, mTOR signaling, AMPK, and sirtuins (35). The reduction in the activity of this nutrient sensing network has an influence on numerous processes, in addition to the metabolism modulation during aging, such as resistance to various stress factors, activation of repair mechanisms, stimulation of autophagy or control of inflammation. Although it is not directly linked to the transformation of SNC, when these other pathways or hallmarks are affected, their relationship with the increase in the SNC is clear (36,37).

MITOCHONDRIAL DYSFUNCTION

There has been evidence for some years that the decline in mitochondrial function with aging may contribute to age-associated dysregulation of energy homeostasis and increased predisposition to age-related diseases. These disruptions are the result of various intra- and extracellular stressors including mtDNA mutations, nuclear genomic instability, reduced mitochondrial biogenesis, defective mitophagy, mitochondrial dynamics, and altered regulation of the electron transport chain, among others. Understanding the role of mitochondria, in addition to serving as a powerhouse for the cell, its dysfunction with aging also

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has implications for chronic inflammation, autophagy, retrograde nuclear signaling, and therefore senescence (38,39,40).

STEM CELL EXHAUSTION

With aging there is a systemic decline in tissues ability to regenerate. The decline in stem cell function associated with age can be observed in different cell populations, including hematopoietic, intestinal, satellite, neural, hair follicle, melanocytic, and germ stem cells (41). The exact mechanism by which there is a decrease in the duplication capacity of stem and progenitor cells is still unknown, but the most common mechanisms of aging in stem cells is explained by some intra- and extracellular factors such as telomere attrition, molecular damage, epigenetic changes and poor regulation of some cellular homeostasis pathways (42). No direct relationship with the SNCs has been found for this hallmark; however, both share several common causal factors.

ALTERED INTERCELLULAR COMMUNICATION

Endocrine, neural, and neuroendocrine pathways provide cues to the cells to respond effectively to environmental changes. Aging leads to a systemic dysregulation of effective intercellular communication. A key consequence of these regulatory failures is the increase of proinflammatory cytokines secretion, interferons activation, alterations in the autophagic response and an increase in the SNC load and consequently of SASP (43). The primary causes of such alterations are cell intrinsic, as this is particularly well documented for the SASP, which affects various intercellular communication pathways and may be co-responsible for the phenomenon of “contagious” aging stimulating an increase in SNC (44,45).

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CHRONIC INFLAMMATION

Age-dependent chronic inflammation "inflammageing" is implicated in a wide range of age-related diseases, in addition to being key in the development and overexpression of most of the hallmarks of aging. Aging is correlated with high levels of inflammatory blood mediators, such as IL-1, IL-6, C-reactive protein, IFNα and many others (46,47). Overexpression of these proinflammatory factors may be secondary to epigenetic dysregulation, deficient proteostasis, or disabled autophagy, leading to an increase in SNC. As a consequence, SASP has been proposed as a plausible link between cellular senescence and "inflammageing" (48,49).

DYSBIOSIS

Over recent years, the gut microbiome has emerged as a key factor in many physiological processes such as nutrient digestion and absorption, protection against pathogens, and the production of essential metabolites including vitamins, amino acid derivatives, secondary bile acids, and short-chain fatty acids. The intestinal microbiota also sends molecular signals to the peripheral and central nervous system, as well as other distant organs, strongly impacting the overall maintenance of the individual's health (50). Recent studies have allowed the identification of very notable changes with age in the intestinal microbiome, noting in particular the loss of species diversity and changes in the microbiome population, which have shown to lead to a state of inflammation (51).

Once the evident relationship between the SNC and the other hallmarks of aging has been established, in most of these as a consequence of their effects, cellular senescence could be suggested as a determining biomarker to measure the progress or status of the hallmarks within Chronological age as a quality metric for

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healthy aging. It is important to highlight that most of the mentioned studies focus on identifying a biomarker at a specific point in life, instead of evaluating how they change over time (52).

In general, a biomarker is defined as any substance, structure or process that can be objectively measured in the body or its products, and evaluated as an indicator of normal biological processes, pathological processes or in response to pharmacological therapeutic interventions (53). The most reliable approach currently available for the measurement of a "senescence state" involves the combination of semi-selective markers since none are specific for senescence, which include SA-β-Gal, lipofucin, loss of HMGB1 or lamin B1, elevated levels of cell cycle inhibitors -such as p16INK4A, p14ARF or 19ARF, as well as p21- or commonly observed SASP factors (54,55,56).

The recent finding that the SNC can potentially be eliminated for therapeutic benefit without implying negative effects has opened the doors to the development of different agents and strategies to specifically target the SNC for the prevention and treatment of aging-related diseases (57,58,59).

In general, these strategies consist of selective SNC killing, called senolysis, SASP neutralization, and immune-mediated SNC killing. Between senolysis and SASP suppression, senolysis has held the best therapeutic promise for two reasons. The first is that the permanent removal of SNC leads to a lasting abolition of the deleterious components of SASP. Second, once a SNC is eliminated, there is no risk of a tumorigenic "escape" from senescence, which would be possible if SNCs were allowed to persist indefinitely. The number of senolytic therapies is still very limited, but some have already been widely used in

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preclinical models of diseases, such as Navitoclax, dual treatment of dasatinib and quercetin, fisetin, cardiac glycosides, among others, giving good results, at least in the increased life expectancy of laboratory mice (60,61,62,63) which could be extrapolated to long-lived species, such as humans.

CONCLUSION

Cellular senescence is an important response to stress and damage, which, in normal physiology, is followed by immune eradication, but in aging or chronic damage fails to be eliminated by immunological mechanisms, and therefore becomes pathogenic due to its abundant secretion of proinflammatory and profibrotic factors (SASP). Currently, the greatest focus given to cellular senescence is in the search for senolytic treatments for diseases. Consequently, it would be opportune to establish research works with methodological strategies that could determine the measurement of biomarkers of senescence, not during a disease, but throughout a period of life, to use it as a quality metric during aging, or a biomarker of "healthy aging" or a prognostic biomarker, which could also determine a starting point for the use of antiaging interventions (senolytics, metformin (64)).

However, we still encounter limitations, since most of the markers currently examined as senescence are more focused on diseases. The senescence biomarkers currently described in the literature do not meet all the criteria to be an ideal biomarker of aging and are not very specific. The selection and identification of reliable biomarkers and the use of reproducible methods could help to achieve a better understanding of the complex process of aging and cellular senescence. Despite the most recent findings at the cellular and molecular level, understanding of the aging process is still limited.

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