

The Aging as a Consequence of Diverse Biological Processes

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Abstract There are many theories that have proposed in order to understand the aging process, and the interpretation of these theories does not reflect an unified concept. With aging, the loss of functional and developmental capacity is evidenced, this reflecting a loss of operational ability of different cells, which are unavailable to function under the gene and environment pressure. Among the mechanisms of homeodynamics, the repair and synthesis of DNA, the capacity to detect and depure proteins, lipids, organelles and defective cells, amongst others, are all well described. The process of homeodynamics also works to maintain proper immune function that is capable of defending against pathogens and recognizing self-antigens in order to prevent the development of auto-immunity and to maintain a controlled inflammatory response. Based on this fundamental concept of homeodynamics, it has been possible to explain the mechanisms that contribute to the process of aging, in contrast to the physiological maintenance of the different pathways (e.g., DNA damage, DNA errors, free radicals, mitochondrial damage, injury/cell insult and theories of immunosenescence) and how these same maintenance pathways cause cells to respond to different stressors with apoptosis, senescence and repair. In this article, we review the theories of apoptosis, senescence and cell repair within the context of their role in the normal aging process.

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Introduction

There are many theories proposed in order to understand the aging process, and the interpretation of these theories does not reflect a unified concept. Aging can be defined as a change in the cellular homeostatic mechanisms in response to apoptosis, senescence and repair; it is, additionally, understood as a response to immune activation and the effects of inflammation over time (Fedarko 2011). Optimal cell function will reflect the dynamic work of multiple “tracks of maintenance” in order to acquire an adequate homeostasis, hinting that biological systems are dynamic, having the ability to self-organize according to the loss of stability in their environment (Lloyd et al. 2001). Interestingly, the amount of cellular damage required to cause a physiological alteration has not yet been determined. Some systems have, however, a cellular redundancy providing a necessary physiological reserve, which allows them to offset the own changes related to aging. This is the reason why the brain and skeletal muscle have more neurons and myocytes, respectively, than those that would be strictly necessary in order to survive (Lipsitz 2002). Trying to determine the crucial point where the cumulative functional loss of old age exceeds the cellular capacity for repair, which dictates when the fragility syndrome of the elderly appears, has been, and remains, of great interest for scientists. In 2009, a cross sectional study, which attempted to answer this question, was undertaken using a sample of 1002 women (Fried et al. 2009). In this study, 12 different cumulative measures evaluating physiological dysfunction in six different systems (Hematologic, inflammatory, hormonal, adipose tissue, neuromuscular and micronutrients) were evaluated. The authors found that there was a linear relationship between the abnormal systems and the development of fragility, independently of age and comorbidities. Abnormal results in three or more systems were interpreted as a strong independent predictor of fragility independent of the abnormality in any particular system. These findings support the idea that when physiological deterioration reaches a critical level, the fragility of the elderly becomes evident.

Among the mechanisms of homeodynamics, the repair and synthesis of DNA, the capacity for detecting and depure proteins, lipids, organelles and defective cells, amongst others, are all well described. The process of homeodynamics also works to maintain proper immune function; to enable the capacity of the organism to defend itself against pathogens; to recognize self-antigens (thus preventing the development of autoimmunity); to develop immune responses against malignant cells; and to maintain a controlled inflammatory response. Based on this fundamental concept of homeodynamics, it has been possible to explain the aging process as a mechanism different from the physiological maintenance of the different pathways (e.g., DNA damage, DNA errors, free radicals, mitochondrial damage, injury/cell insult and theories of immunosenescence) and to understand how these same maintenance pathways cause cells to respond to different stressors through apoptosis, senescence and tissue repair. In addition, the way they converge in turn triggers the immune system in a perpetuated inflammatory response is also described (as shown in Fig. 1). If any of these intrinsic cell processes fails, the cells undergo a process of proliferative

transformation (neoplastic) with further compromise of organ function and survival. Thus, an exaggerated expression of apoptosis can phenotypically express as an atrophy of the tissues or organs, increased cell senescence or expression of proinflammatory cytokines. This orchestration of cellular mechanisms has been implicated in normal aging and, once again, it has been found that the balance between them will determine the phenotypic expression in terms of functional changes in various systems of the body. It is important to understand how each of these theories support the global understanding of getting old; they are currently seen in the same model. Interestingly, a pro-inflammatory state is the final pathway of several processes, such as cell death and oxidative stress, among others.

The Effects of Aging

Life began on earth more than 3 billion years ago when deoxyribonucleic acid (DNA) acquired the ability to replicate and mutate thus making the transmission of genetic

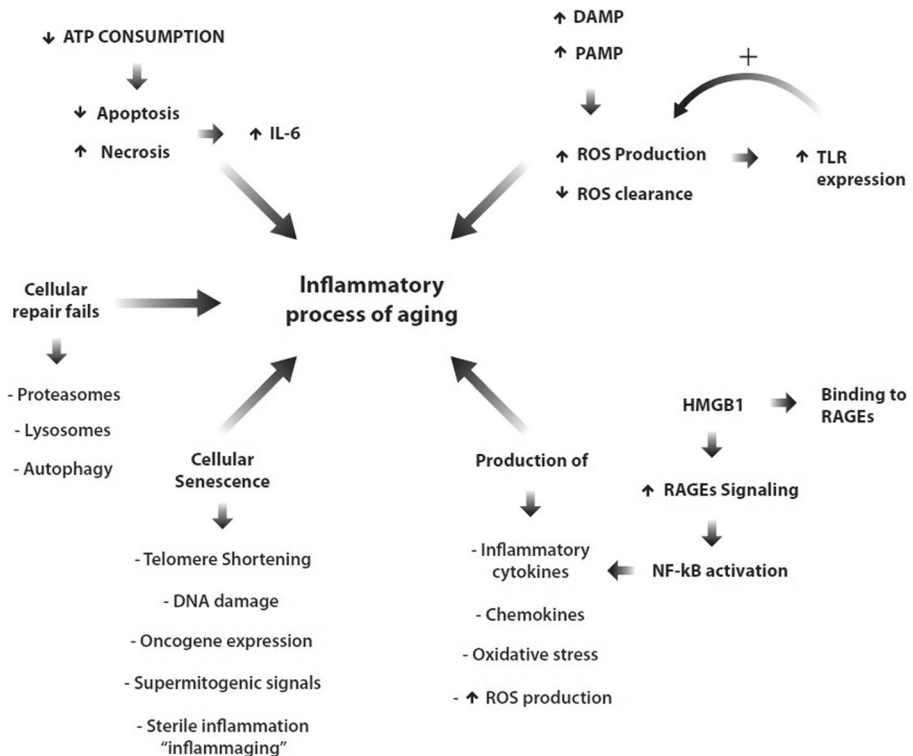


Fig. 1 Comprehensive description of the mechanisms influencing the aging process. There are different pathways, such as DNA damage, DNA errors, the production of free radicals, mitochondrial damage and theories of cellular senescence that are implicated in the inflammatory process of aging. It is hypothesized that these mechanisms cause the cells respond with either apoptosis, senescence or repair. DAMP: Damage-associated molecular pattern molecules; PAMP: pathogen-associated molecular patterns; ROS: reactive oxygen species; HMGB1: High-mobility Group Box 1 proteins; RAGEs: Receptor for Advanced Glycation End products; TLR: Toll-like receptors; IL-6: interleukin 6; NF-kB: Nuclear Factor kB

information to offspring possible, leading to the generation of biodiversity (Landenmark et al. 2015). The lack of a universal definition of life is a problem for biology, leading to multiple different definitions for ‘life’. Probably the concept of ‘life’ requires a general conceptual framework rather than a precise definition. The answer should, therefore, come from the union of different specialists working on different problems and different perspectives. The diversification of life on Earth was the result of a complex evolutionary process, not a single event derived at random. Based on this concept, normal aging is associated with a progressive decrease in the ability to adapt to different conditions in the environment that finally cause morphological and physiological changes which lead to the development of fragility and cause inevitable death (Ruiz-Mirazo et al. 2004).

The search for the “Elixir of Life” was one of the goals pursued by many alchemists as a remedy to cure all diseases and thus attain eternal life. Ancient cultures, such as those in China and India, crossed seas trying to find this secret potion, with people ingesting minerals such as cinnabar, hematite, jade and especially gold with the belief that this would help them to experience a life that lasted longer than normal (Ettington 2010). The advent of Buddhism, Hinduism and Christianity, amongst other religions, subsequently made the “Elixir of Life” craze decline, as these religions advanced the idea of immortality (Fahlbusch et al. 1998).

Fleeing from religious precepts, the so-called Alchemists, based on the Aristotelian doctrine that postulates “all things tend to reach perfection”, laid the foundations of what was then the modern scientific development. Paracelsus was the most important representative of this group of thinkers, and he argued that disease came from the outside; based on this model, he created remedies from various minerals with a view to helping the body defend itself. He also identified the characteristics of many diseases such as goiter and syphilis, and he used ingredients like sulfur and mercury to combat them. Many of his remedies were based on the belief that ‘like cures like’, and today his work is still considered a precursor to homeopathy. Although the writings of Paracelsus contain elements of magic, his work advanced medical thinking and began a more scientific approach to the understanding of disease and the aging process. This universal quest as to how to slow down, and generally try to avoid, the multiple complications of aging has been a universal quest of mankind (Leicester 1971).

The expectancy and quality of life have increased significantly in recent years compared to the past. This can be considered a consequence of socioeconomic development and a success for public health policies. The elderly population is growing rapidly; it is estimated that, by 2050, 2 billion people will be elderly (Phillips and Kinsella 2005). It is estimated that between a quarter to half of the world’s population over 65 years old is fragile, putting them at high risks of falls, disability, dependence of caregivers and a high probability of death (Clegg et al. 2013). This state of fragility is understood as a state of increased vulnerability. Fragile individuals experience poor responses in their homeostatic capacity after a stressful event (for example a urinary tract infection, a minor surgical procedures or the introduction of a new drug etc), and, from the clinical point of view, after such a stressful event, many elderly people are subsequently characterized as suffering from extreme fatigue, unexplained weight loss and susceptibility to recurrent infections. Further, their gait and balance can be altered, which is an additional important risk factor for falls. Delirium (sometimes called ‘acute confusional state’) is related to an integral function of an altered brain. Importantly,

almost 30 % of elderly people admitted to hospital develop delirium, which is an independent risk factor for adverse events (Eeles et al. 2012). Finally, fragility in the elderly is characterized by fluctuations in their degree of disability, with days when they are able to be independent in their activities and days when they are not.

Centers for anti-aging research, such as the National Institute of Aging in North America, explore different strategies to prevent and delay this inevitable process; such centers have been established all around the world (Fort 2011). Aging is not, currently, considered a disease and, for this reason, it is not possible to conduct research studies, to evaluate drugs or interventions that may impact the natural course of this process. On the other hand, prevailing political and societal opinions suggest that the elderly cannot contribute anything to society, and we have limited ourselves to see the old human being as an individual with disabilities which has meant that the idea that aging is a disease that might be curable has not received merit in society as a whole nor in the general academic community. This idea is based on the thinking of some scientists who see the human being as a machine capable of restoration and repair, suggesting that aging, and therefore letting people die, should not be allowed (Fort 2011). The problem that this “science fiction” world would face, if this happens, would be serious overpopulation leading to the exploitation of the multiple systems that try to maintain society in balance. Independent of any concept - social, philosophical, religious and/or scientific - we believe that the aging process must be viewed holistically as an aspect of life that is inevitable, and necessary, where multiple physiological systems are interrelated through a genetic base and which is affected by environmental factors in combination with epigenetic mechanisms which regulate the expression of different genes in cells. The process of aging must, also, be faced as the inevitable - normal - course of an ancient evolutionary process.

In this review, we explore the different concepts that are believed to be involved in the aging process, and look at how immunological and auto-inflammatory mechanisms affect this process.

Cell Death

Apoptosis, the self-organized process of cell destruction, is crucial for survival and for the formation of multicellular organisms (Haanen and Vermes 1996). In adults, apoptosis is a vital physiological process which eliminates cells that are no longer required, maintaining tropism and tissue function (Mondello and Scovassi 2010) and removing damaged and dysfunctional cells (Muradian and Schachtschabel 2001). It has also been shown that apoptosis is an important cellular defense mechanism in the maintenance of genetic stability and it has been seen how people who lived longer, have a better potential to regulate apoptosis (Franceschi et al. 1992). At any particular time, these regulatory mechanisms may fail and this failure may be involved in pathological processes, including the development of immunological autoreaction. Apoptosis can be triggered by different external stimuli, including, for example oxidative stress or intrinsic changes in the cell. This stimulates a number of mechanisms in the cell surface receptors that activate different intracellular pathways converging on the mitochondria, leading to the signal activation of caspases (a group of proteins belonging to the group of the cysteine - proteases characterized by having a cysteine residue which mediates the disruption of other proteins and DNA). Apoptosis is a

process that requires energy and hence ATP consumption (Richter et al. 1996). It has been suggested that the energy reserve in elderly people is depleted because of a dysfunction in their mitochondria and/or mutations in their DNA (Wallace 2005) and, as such, the normal processes of apoptosis (chromatin condensation, formation of vesicles and activity of hydrolytic enzymes), which are mediated by ATP consumption, cannot be carried out. As a compensatory mechanism, cell death is mediated, mainly by necrosis (Haanen and Vermees 1996). We could argue, therefore, that an abnormal increase in the level of apoptosis leads to tissue degeneration (sarcopenia, for example, is mediated by apoptosis) (Mondello and Scovassi 2010); it is also known that low levels of apoptosis lead to the accumulation of dysfunctional cells and/or the persistence of immune differentiated cells. In this manner, the loss of the ability to develop apoptosis will stimulate a chronic inflammatory process, which probably reflects the fragility and self-functional decline that are representative of aging. As discussed below, this pro-inflammatory state is characterized by a typical phenotypic change in the aging cell, known as senescence, which is characterized by high levels of interleukin (IL)-6 (IL6), levels of which have an inverse correlation with apoptosis (Muradian and Schachtschabel 2001).

Oxidative Stress

In all of the theoretical models described, the production of free radicals and their accumulation leads to cell dysfunction and death. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of a biological system to detoxify these intermediate reactions or repair the resulting damage. In turn, the ROS has also been identified as an important signaling molecule in various pathways regulating both death and cell survival (Hormesis). ROS are free radicals that contain an oxygen atom. These small molecules are known as superoxide anion (O_2^-), hydroxyl radical (OH), hydrogen peroxide (H_2O_2) and oxygen (O_2). These ROS are normal byproducts of normal oxygen metabolism and have important roles in signal transduction; but they can also contribute to excessive dysregulation of signal transduction and/or oxidative damage to cellular macromolecules (lipids, proteins, DNA, RNA and carbohydrates). The main sources of ROS are the mitochondria and NADPH (nicotinamide adenine dinucleotide phosphate oxidases) (Fig. 2). In animals, ROS influence intracellular signaling cascades such as PTP (Protein tyrosine phosphatases), PTK (Tyrosine Kinase), PKC (Protein Kinase C), MAPK (mitogen - activated protein kinase) and nuclear Factor κ B (NF- κ B). The internal environments of all living cells in the organism remain in reduced state. This process is achieved and maintained by enzymes that uphold a “metabolism-derived input of energy”. Increased and sustained levels of oxidative stress and related mediators have an important role in many chronic human diseases, such as atherosclerosis, diabetes, cardiovascular disease, cancer, neurodegenerative diseases, chronic liver disease and chronic pulmonary diseases. We believe that all these diseases could be clustered within a single group called simply “cell aging” and thus, in this perspective, treatment could have a more timely approach and be less dispersed, in order to treat ‘aging’ as a holistic entity. Inflammation appears as a self-defense mechanism of the cell in response to different damage signals. These signals could be intrinsic cell signals such as DAMPS (Damage Associated molecular pattern molecules) or extrinsic cell signals such as PAMP

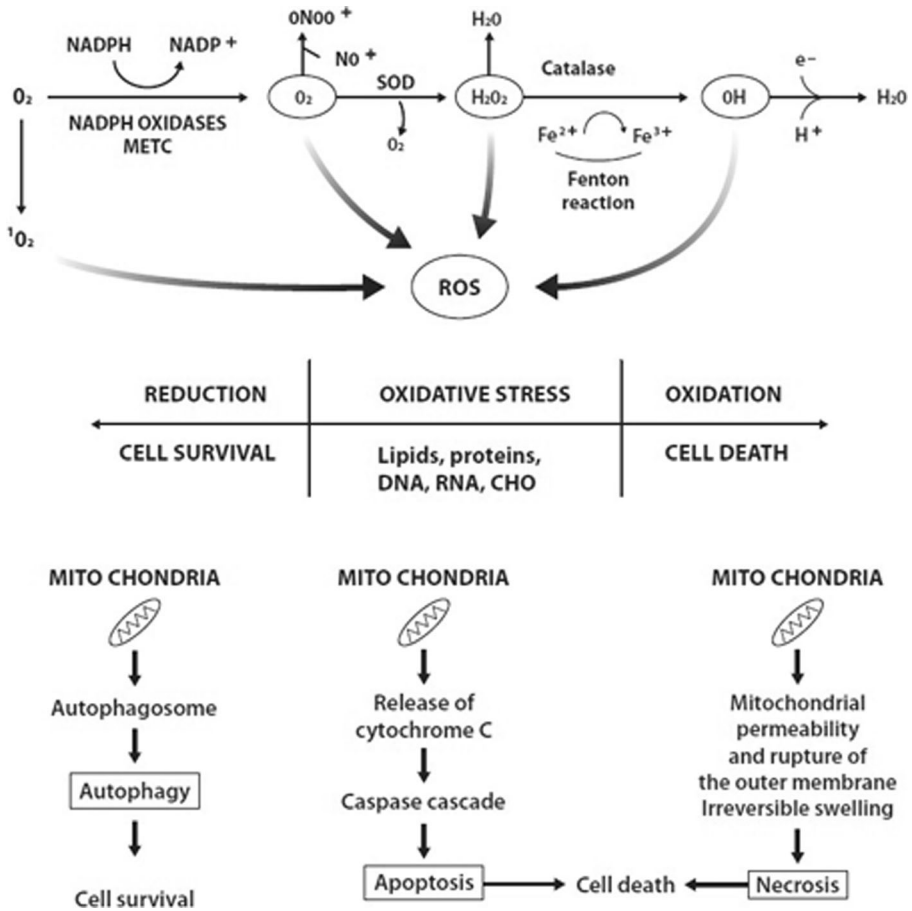


Fig. 2 Description of the source of ROS and intracellular activation pathways. The main source of ROS is the mitochondria and NADPH. ROS are known as superoxide anion, hydroxyl radical, hydrogen peroxide and oxygen (O_2). These compounds normally have a role to play in signal transduction but a deregulation of signal transduction and/or oxidative damage to cellular macromolecules (lipids, proteins, DNA, RNA and carbohydrates) can lead to cell death. NADPH: Nicotinamide adenosine dinucleotide phosphate oxidase; METC: mitochondrial electron transfer chain; O_2^- : superoxide anion; ONOO: peroxynitrite; NO: nitric oxide; H_2O_2 : Hydrogen Peroxide; SOD: superoxide dismutase; OH: hydroxyl radical; 1O_2 : Singlet oxygen; O_2 : Oxygen

(Pathogen Associated molecular patterns). Activation of one of these pathways, through receptors on inflammatory cells, induces the generation of ROS. In response to this, activated cells mount an antioxidant response in order to prevent the possible deleterious effects of oxidation. When the repair is completed, the homeostasis is reached again. Research has shown that the intra- and extra-cellular redox state regulates the expression of TLRs (Toll-like receptors), receptors that are responsible for recognition of the patterns of damage (such as the PAMP) and for advanced glycation end products (AGEs). They also affect the structure and function of different proteins, and stimulate the secretion and function of cytokines such as Transforming-Growth Factor 1 (TGF- β 1), IL-1, IL-4, IL-10, S100 protein, TNF and HMGB (High-mobility group box proteins). HMGB-1, also known as anferines, were initially purified from cell

nucleii roughly 40 years ago and were well-known for their rapid mobility on electrophoresis gels (Miyoshi et al. 2006). They are constitutively expressed in the core of many types of cells including cancer cells. These proteins acts as a nuclear DNA chaperone as it is involved in the replication, recombination, transcription and repair of DNA. They also work by enhancing the action of different transcription factors, including p53 (theory of cellular senescence), p73, retinoblastoma protein, members of the Rel/NF- κ B family and nuclear hormone receptors, including estrogen receptors. In addition to its role in the cell nucleus, high motility proteins also have roles in extracellular signaling molecules, DAMP during inflammation, cell differentiation, cell migration, cell proliferation, tissue regeneration and tumor development (Table 1 and Fig. 3).

RAGEs

Discovered and identified in the 1990s (Brett et al. 1993, Neeper et al. 1992), the receptors for advanced non-enzymatic glycosylation (RAGEs) are known as multiligand receptors that interact with three-dimensional structures rather than with amino acid sequences (i.e., they interacts with molecular patterns rather than with a specific ligand), giving it the capacity to join several exogenous and endogenous ligands. The RAGEs have been involved in many acute and chronic inflammatory processes. Among the identified ligands are the products of advanced non-enzymatic glycosylation (AGES), and also the products of oxidation of proteins, lipids and polynucleotides. It has also been demonstrated that the main RAGE ligands, apart from AGES, are the HMGB1, S100 proteins fixing calcium –(also called calgranulins), beta amyloid peptide and the Mac-1, a beta 2 integrin (CD11b/CD18). This interaction Rinduces signals that cause cellular changes that lead to inflammation (Fig. 4). This property, along with the various endogenous ligands, makes RAGEs a major factor in the development and progression of inflammatory diseases that are associated with old age (Herold et al. 2007). Although stimuli to RAGE may be variable, all of them converge in the IKK (phosphorylating kinase complex inhibitor of the transcription factor NF- κ B in the cytoplasm), which releases the NF- κ B and which is then subsequently degraded. Within this process, the NF- κ B translocates to the nucleus, inducing the synthesis of various pro-inflammatory factors (such as the expression of adhesion molecules, cytokines, chemokines, and oxidative stress), increasing the expression of the NADPH oxidase, which leads to an increase of superoxide anion. At the same time, the DNA encoding RAGE is expressed again, acting as a positive feedback mechanism increasing the inflammatory process. RAGE and TLRs share certains ligands, such as

Table 1 Functions of High-Mobility Group Box 1 (HMGB1) as a DNA chaperone and DAMP signal

DNA chaperone	DAMP signal
Replication	Inflammation
Recombination	Immunity
Transcription	Chemotaxis
Repair	Regeneration

DNA desoxyribonucleic acid; *DAMP* Damage-associated molecular pattern molecules

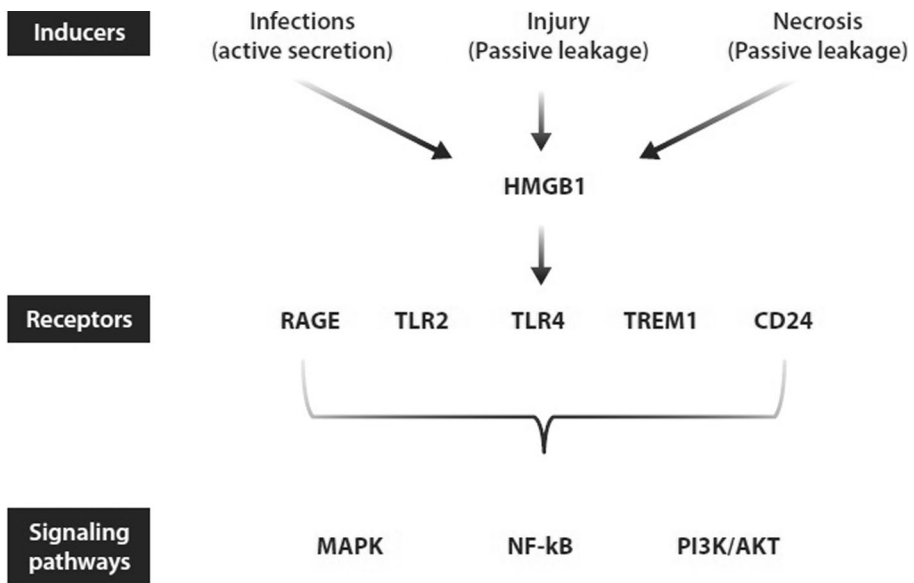


Fig. 3 High mobility group box 1 inducers, receptors and effects. HMGB1 protein acts as a nuclear DNA chaperone, involved in replication, recombination, transcription and repair of DNA. There are different inducers of its expression through diverse receptors activating intracellular signaling cascades such as MAPK (mitogen - activated protein kinase), a PI3K/AKT/mTOR and nuclear Factor kB (NF-kB) pathway

HMGB1, but unlike RAGE, the TLRs interaction with other RAGE ligands such as AGEs, S100 and Beta amyloid peptides has not been reported. It has also been demonstrated that RAGEs and TLRs have different affinity for a common ligand. Endogenous ligands may have a lower dissociation constant when interacting with RAGE than they do with TLRs (perhaps causing chronic inflammation) (Chavakis et al. 2004). Ligands originating from pathogens, however, bind more tightly to TLRs than RAGE, inducing acute inflammatory states. The affinity between ligand and receptor can determine the signal strength and the signaling pathway.

Unlike TLRs, RAGEs contain a cytosolic domain with no homology to TLRs, which could generate different signaling pathways and regulation. In addition to the effects produced by the activation of RAGE, this molecule can act as an adhesion receptor on leukocytes, allowing the extravasation of these cells across the endothelial barrier. To explain this situation, Chavakis et al. demonstrated, in a murine RAGEs knock-out (*RAGE^{-/-}*) model, that leukocyte infiltration is decreased after an inflammatory stimulus, an effect that is reversed by inducing expression of RAGEs (Chavakis et al. 2004). This study suggests the importance of RAGEs in tissue infiltration by leukocytes, as seen in the early steps of atherogenesis (Hansson and Libby 2006). RAGEs thus represent an alternative for adhesion molecules such as ICAM-1 (intercellular adhesion molecule - 1) in leukocyte infiltration. Based on this pro-inflammatory concept, the association between arterial changes and AGEs has been demonstrated in animal models and in humans. Research *in vivo* has shown that the administration of HMGB1 induces neutrophil adhesion to endothelium mediated by ICAM-1 or fibrinogen (Orlova et al. 2007). HMGB1 may also increase the inflammatory process via the activation of TLRs 2 and 4 by inducing the expression of adhesion

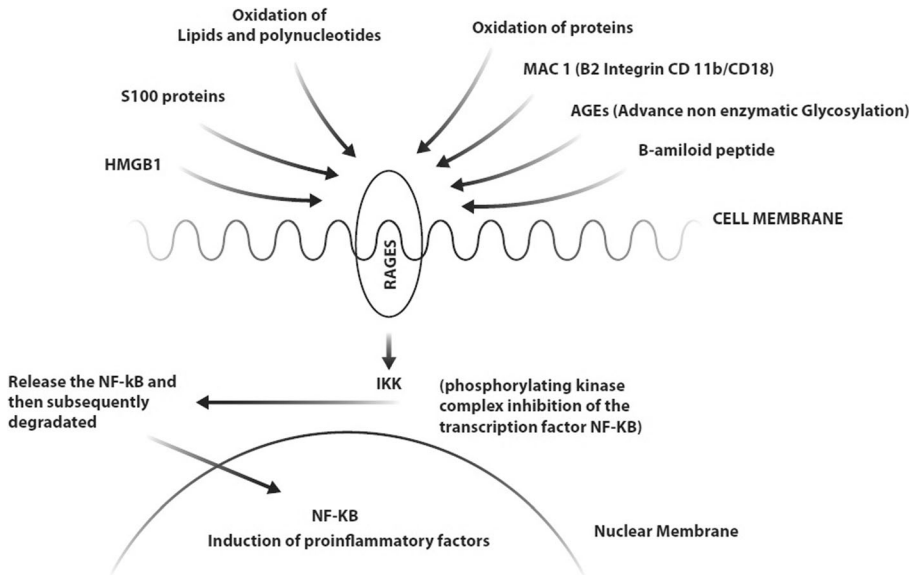


Fig. 4 RAGEs as inflammatory mediators. The RAGEs have been involved in many acute and chronic inflammatory processes. The identified ligands are the products of advanced non-enzymatic glycosylation (AGES), the main ligand; and other like HMGB1, S100 proteins, beta amyloid peptide, the Mac-1, oxidation of proteins, lipids and polynucleotides. The activation of RAGE converges in the IKK activation, which releases the NF- κ B and induction of pro-inflammatory factors

molecules on leukocytes and endothelium (Park et al. 2006, Park et al. 2004). It has been reported that, during aging, the arterial wall has a profile characterized by elevated proinflammatory proteins of the extracellular matrix and high levels of different chemokines such as MCP-1 (monocyte chemoattractant protein - 1) (Wang et al. 2007). HMGB1, besides interacting with RAGE to induce a proinflammatory process, also has a chemotactic activity, facilitating the passage of leukocytes to tissues, as already outlined. It is likely that the activation of RAGEs, besides inducing inflammation, is also involved in tissue remodeling, events that may induce the abnormal proliferation of vascular cells and the formation of atherosclerotic plaques with consequent thickening of the arteries and heart disease.

Senescence as a Pro-Inflammatory State

Aging is the most important risk factor for the development of chronic diseases, such as atherosclerosis, dementia, cancer, renal failure, macular degeneration, sarcopenia, increased susceptibility to infections, osteoporosis, and vascular disease, amongst others. New perspectives on this situation, comprising the different theories that attempt to explain its ontogeny, suggest that aging could become a modifiable risk factor. One possible explanation for this situation is the chronic non-microbial inflammatory state seen in different tissues in aging individuals. Different markers of inflammation such as IL-6, TNF- α and other pro-inflammatory cytokines, have the highest correlation with physiological fragility syndrome, indicating the vulnerability of the elderly population to surgical, infectious or traumatic stressors. We can conclude, from this, that

treating these entities one by one may not be sufficient to achieve overall improvement in terms of life expectancy. If, for example, cancer were eliminated as of the main causes of death, human survival would increase only 3–4 % (Olshansky et al. 1990).

One theory explaining this proinflammatory state is *cellular senescence*, elucidated in the 1960s as Hayflick-Moorhead (Hayflick and Moorhead 1961) or replicative senescence, which refers to the loss of the ability to divide and arrest cell proliferation. It is an intrinsic mechanism of the cell to defend against potentially cancer-causing events. It is noteworthy that senescent cells are part of the phenotypes of aging and various chronic pathologies previously described (Tchkonina et al. 2013) and that the elimination of these cells can eventually retard cellular dysfunction associated with aging, at least in mouse models (Baker et al. 2011). This senescent phenomenon is limited by the number of telomeres at the end of cellular DNA, meaning that each subsequent cellular division will result in telomere shortening and that, when it reaches the critical height, the cellular DNA replication machinery is affected, entering in to an irreversible arrest proliferation state, leading to altered intrinsic function and, in some cases, to resistance to apoptosis. Arrest proliferation is maintained by some inhibitors of cyclin-dependent kinases known as p16 and p21 that modify the cell cycle (Ohtani et al. 2004).

Interestingly, lymphocytes are amongst the few cell types that can actively elongate telomeres through the action of telomerase (Hohensinner et al. 2011). Senescence is, therefore, of particular relevance for cells that are long-lived, as is the case for memory T lymphocytes, the carriers of immune memory. T cells are known to be able to live for over a decade. Nevertheless, they are somatic cells and are, therefore, not immortal. Aging T cells are characterized by the absence of the co-stimulatory receptor CD28 (Weng et al. 2009). CD28 negative T-cells have a distinct gene expression profile, including genes generally associated with proinflammatory activities. Aged T cells may thus have a critical role as inflammatory amplifiers and may, therefore, represent a major mediator of the aging-associated inflammatory syndromes. They produce IFN γ in higher amounts than their CD28 positive counterparts (Liuzzo et al. 2000). An important feature of CD28 negative T cells is the expression of different membrane receptors that are usually reserved for NK cells, including CD158A, CD158B, CD158J, DAP12, CD94 (or KLRD1), and CD244 (Fasht et al. 2010). Generally, senescence-associated inflammation has been connected to a 2–4-fold increase in the levels of acute-phase reactants, such as C-reactive protein and interleukin-6, and it is possible that, in future, biomarkers will be developed that monitor the aging process (Johnson 2006). Increased inflammatory activity is now recognized as a hallmark of a number of age-related diseases, such as atherosclerosis and insulin resistance (Johnson 2006; Donath and Shoelson 2011).

These hits activate tumor suppressor pathways, known as p53 and p16INK4a, and possibly other pathways that initiate the senescence response. Once the senescent response has been initiated, it takes days to weeks until all the mechanisms are put in place in a full and irreversible manner. It seems that senescent cell phenotypic change is a process that is led by intracellular signals that are included among ROS coupled to DNA damage responses (DDRs) NF-kB, TGF-B, as well as IL-1 alpha, IL-6 and the CCAAT enhancer-binding protein β (C / EBP- β)” (Kuilman et al. 2010, Freund et al. 2010). During this process, senescent cells reorganize chromatin by forming heterochromatin, a process that involves extensive changes in gene expression. As a result, cell size increases and the protein content changes, in addition to changes in the morphology of the organelles. The common result of aging tissues is a chronic inflammatory

condition of low intensity, called sterile inflammation (indicating the absence of detectable pathogens) or “inflammaging” (Chung et al. 2009). This pro-inflammatory state may trigger disease through two main mechanisms: 1) by infiltration of immune cells to healthy tissues, which releases toxic moieties and/or reactive species and 2) through the effect of inflammatory cytokines and chemokines on phenotypic changes in neighboring cells that are independent of the immune system. IL-6 and IL-8 can, for example, stimulate angiogenesis, alter cell-cell contact, affect macrophage function, induce innate immune responses, and promote the migration and invasion of epithelial and endothelial cells (Tchkonina et al. 2013). Little is known about the source of this sterile inflammation but, independent of the activation pathway, the accumulation of senescent cells in progeroid syndromes causes that these cells acquire a phenotype called SAPS (senescence-associated secretory phenotype) which is characterized by enlarged cells, the presence of beta-galactosidase, increased expression of proteases, inhibitors of the cell cycle and increased expression of proinflammatory cytokines, such as IL-6.

Cellular senescence is a double-edged sword, because its different functions of the phenotype can have positive or negative effects on the living organism. The first concept is *pleiotropic antagonism*. Described as part of the theories of evolution in aging, this concept predicts the existence of a process that was evolutionarily selected to ensure health in the early years of life (i.e., protection against cancer promoting immune responses), but which has deleterious effects on adult life in terms of its role in promoting aging phenotypes and causing disease (Kirkwood and Austad 2000). Secondly, the positive or negative effect of SAPS depends on the particular context. If the SAPS is very pronounced and persistent, it may cause local and potentially systemic inflammation, altering tissue architecture and stimulating the growth of neighboring malignant cells, as has been seen in the elderly, in adults with massive obesity and progeria (Orlova et al. 2007, Minamino et al. 2009). By contrast, a localized SAPS, that is limited in time, can be important in resolving tissue damage, at least in young individuals, being an example of the previously described pleiotropic antagonism.

Senescence Decreases the Cellular Repair Mechanisms

Independent of the apoptosis pathways, cells also have the ability to repair by removing and/or repairing proteins including lipids, organelles and others, through catabolic pathways such as: a) Proteasomes (a protein complex that degrades molecules “tagged” with ubiquitin); b) Lysosomes (organelles that fuse with cell vacuoles, producing enzymatic complexes via the degradation of proteins, polysaccharides, nucleic acids and lipids); and c) the autophagosomes, which sequester cytoplasmic components through phagophore formation (also called the isolation membrane), merging with lysosomes and, through their enzymatic machinery, degrading auto-phagocytosed material (Miyoshi et al. 2006). These catabolic pathways prevent the accumulation of cellular components and/or aberrant molecules or damaged cells. DNA repair fails during the life of each individual and may be a mechanism generated to enable energetic cost savings in an organism that has exceeded the reproductive age. These changes are related to processes linked to aging, susceptibility to tumor development and various forms of immunological autoreaction (Weyand et al. 2003). During aging, the dysregulation of autophagy, proteasomes, and lysosomes will limit the ability of the

cell to remove oxidized and molecularly altered (“unfolded”) proteins and, will also affect the removal of nucleic acids, lipids and polysaccharides. From the histopathological point of view, the accumulation of insoluble substances, such as lipofuscin, a product of the oxidation of fatty acids, is observed. As detailed above, during the process of aging, there is progressive mitochondrial damage by DNA mutations, ROS production or the accumulation of toxic metabolic products. Harman (1956) suggested that free radicals, which are common in living organisms, as a result of environmental triggers such as radiation, toxic exposure and dietary indiscretions, offer a possible explanation for cellular injury. Harman (1956) suggested that when the overproduction of free radicals exceeds the capacity for cellular repair, this can lead to cell death or the death of the organism. While this is a long-established theory, the impact that antioxidant intake can have on preventing the aging process is uncertain, since certain levels of free radical activity are required to perform restorative and physiological functions in human beings (Bjelakovic et al. 2012), a process called *hormesis*.

Senescence as a Consequence of Caloric Intake

Concerning our modern lifestyle, which is poor in physical activity and rich in a full diet of carbohydrates and lipids, an additional theory - the process of glycation and lipo-oxidation - has been suggested to explain senescence. This theory proposes that AGEs may cross-link proteins, making them ineffective in their core functions, which is represented through the presence of wrinkles, inflammation, cataracts, atherosclerosis, and endothelial dysfunction, amongst others (Vlassara 2005). This theory has gained evidence from the diabetic population, which, from the clinical point of view, has a high level of dysfunction across multiple systems, including alterations in vascular tone, endothelial dysfunction and premature atherosclerosis, all as a consequence of having an excess of “sugar” to carry the glycation process. Homeostasis is normally maintained by autophagy mediated by mitochondrial turnover and, through experiments in other living beings (such as yeast, worms, flies, rodents and non-human primates), it has been shown that a calorie-restricted diet will decrease AGEs, resulting in an optimal cell environment and thereby offering increased longevity (Bordone and Guarente 2015). This concept of calorie restriction dates from 1934, when different observations in experiments with rats showed that those with calorie restriction, but proper nutrition, were able to live almost twice as long as those rats receiving a conventional diet. The first multicenter controlled study that is systematically investigating, in humans, sustained calorie restriction of 25 % and the impact on aging in relatively healthy and non-obese people is the phase II study CALERIE (Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy). This study recently enrolled 10,856 individuals, all of whom met certain inclusion criteria, and appropriate follow up only of 218 people (Stewart et al. 2013). The study aims to explore the effects of 2 consecutive years of calorie restriction on aging in humans and, as such, is similar to the studies undertaken using other animals. Some beneficial effects of calorie restriction have been demonstrated previously, such as reductions in atherosclerotic disease (Fontana et al. 2004), reduction of body mass, memory improvement in the elderly (Witte et al. 2009), decreases in blood pressure and in LDL and total cholesterol, amongst others. Additionally, a decrease in total body

temperature, possibly indicating reduced metabolic activity, has also been shown to decrease oxidative stress and cell division. Plasma levels of fasting insulin and blood glucose decreased along with pro-inflammatory markers such as ultrasensitive C-reactive protein (Fontana et al. 2004). From a molecular standpoint, calorie restriction activates silent receptors called SIR2 (Silent information receptor 2) and SIRT1, through activation of the SIRT7 genes, which produce proteins known as sirtuins which, by epigenetic phenomena, regulate the expression of certain genes through the histone deacetylase activity of NAD-dependent (Sato et al. 2010). It is, therefore, very likely that the final results of CALERIE will be encouraging.

The concept of calorie restriction is perhaps the most studied theory to explain anti-aging and the research has attempted to evaluate other treatment options that may mimic the beneficial effects of calorie restriction, whilst still allowing people to eat what they want. Resveratrol, known as phytoalexin, is a substance that is found in grapes and grape-derived products, such as wine, juice, and other foods, such as oysters, peanuts and walnuts. It seems that resveratrol simulates aging pathways proposals on caloric restriction, stimulates the production of sirtuin genes, among other beneficial activities, such as antioxidant effects (Hung et al. 2000), antiviral (Docherty et al. 2006), anticarcinogenic (Leone et al. 2010), antidiabetic (Deng et al. 2008), anti-inflammatory (Gentilli et al. 2001), cardioprotective (Hung et al. 2000) and neuroprotective (Karuppagounder et al. 2009). Production of resveratrol is a defensive response to a hostile and stressful environment. Animal models have shown that resveratrol has many benefits in terms of anti-aging and aiding with obesity (Howitz et al. 2003; Valenzano et al. 2006). Whilst studies demonstrating the benefits of resveratrol in humans are lacking, from an epidemiological point of view, the “French Paradox” shows that the consumption of substances that stimulate the production of sirtuins (such as resveratrol) may be beneficial. Observational analyses show that the French population has better health and vitality compared to other populations, despite the chronic and regular consumption of wine and food that are considered inconsistent with proper health practices. Another candidate that mimic calorie restriction pathways, but which has not yet been shown to increase life expectancy in humans, is Rapamycin, which inhibits the expression of TOR (Target of Rapamycin) genes. TOR genes appear to control aspects of the production of proteins in the same manner in which calorie restriction reduces the production of proteins under conditions of stress (Stanfel et al. 2009). Furthermore, metformin has a large impact on increasing life expectancy by reducing the deleterious process of diabetes. It also acts on multiple pathways by altering the effects of high calorie intake by increasing gene expression of beneficial proteins, reducing, for example, the presence of enzymes that increase fatty acid oxidation and causing consequent delays in cell death (Collier et al. 2006). It also activates the AMP-K (Adenosine monophosphate-activated protein kinase), influencing cell repair enzymes, which increases peripheral insulin sensitivity (Winder and Hardie 1999), decreases cortisol levels and increases levels of testosterone and growth hormone.

Conclusion

Normal aging is associated with a progressive decrease in the ability to adapt to different environmental triggers that cause morphological and physiological changes

leading to the development of diseases and to inevitable death. Multiple theories have been described that try to understand this process and, as this work shows, none of these theories, individually, clarify all the multiple pathophysiological mechanisms involved in aging. Physiological processes, such as cellular mechanisms of apoptosis and necrosis, oxidative stress and the stimulation of signaling pathways, such as DAMPS or extrinsic cell signals such as PAMP, culminate in the generation of ROS, which in turn modulates the expression of TLRs and the activation of RAGEs with molecular patterns with a specific ligand such as AGEs and HMGB1 (amongst others). The aging process leads to a state of cellular senescence, which is characteristic of a purely inflammatory phenotype. All this interaction induces signals that cause cellular changes that lead to an inflammatory phenotype. Among all the diseases of aging, such as atherosclerosis, diabetes, osteoporosis, sarcopenia, dementia and frailty syndromes, we believe that all these diseases could be clustered within a single group called “*cell aging*”. Approaching the problem of aging from this perspective would allow a more timely approach as compared to treating each of the theories separately.

Aging is not, currently, configured as a disease, and the FDA has proposed aging as a natural and inevitable process that meets individual characteristics in order to adapt to a hostile environment. This understanding of aging explains how the epigenetic effects of these environmental pressures may have an effect on cell homeodynamics. Cellular senescence is a double-edged sword, because its phenotype, with different functions, can have positive or negative effects on the living organism. This concept is defined as *pleiotropic antagonism*.

Compliance with Ethical Standards

Conflict of Interest Nicolas Coronel Restrepo declares that he has no conflict of interest. Fabio Bonilla Abadía declares that he has no conflict of interest. Andres Agualimpia declares that he has no conflict of interest. Andrés F. Echeverri declares that he has no conflict of interest. Fabio E. Ospina declares that he has no conflict of interest. Carlos A. Cañas declares that he has no conflict of interest. Gabriel J. Tobón declares that he has no conflict of interest.

Informed Consent As there is no person or personal data appearing in the paper, there is no one from whom a permission should be obtained in order to publish personal data.

Ethical Treatment of Experimental Subjects (Animal and Human) This article does not contain any studies, performed by any of the authors, with human or animal participants and, as such, did not require ethical approval.

References

- Baker, D. J., Wijshake, T., Tchkonja, T., LeBrasseur, N. K., Childs, B. J., van de Sluis, B., et al. (2011). Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature*, 479(7372), 232–236.
- Bjelakovic, G., Nikolova, D., Gluud, L. L., Simonetti, R. G., & Gluud, C. (2012). Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database of Systematic Reviews*, 3, CD007176.

- Bordone, L., & Guarente, L. (2015). Calorie restriction, SIRT1 and metabolism: understanding longevity. *Nature Reviews. Molecular Cell Biology*, 6(4), 298–305.
- Brett, J., Schmidt, A. M., Yan, S. D., Zou, Y. S., Weidman, E., Pinsky, D., et al. (1993). Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. *The American Journal of Pathology*, 143(6), 1699–1712.
- Chavakis, T., Bierhaus, A., & Nawroth, P. P. (2004). RAGE (receptor for advanced glycation end products): a central player in the inflammatory response. *Microbes Infect Inst Pasteur*; 6(13), 1219–1225.
- Chung, H. Y., Cesari, M., Anton, S., Marzetti, E., Giovannini, S., Seo, A. Y., et al. (2009). Molecular inflammation: underpinnings of aging and age-related diseases. *Ageing Research Reviews*, 8(1), 18–30.
- Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *Lancet*, 381(9868), 752–762.
- Collier, C. A., Bruce, C. R., Smith, A. C., Lopaschuk, G., & Dyck, D. J. (2006). Metformin counters the insulin-induced suppression of fatty acid oxidation and stimulation of triacylglycerol storage in rodent skeletal muscle. *American Journal of Physiology. Endocrinology and Metabolism*, 291(1), E182–E189.
- Deng, J. Y., Hsieh, P. S., Huang, J. P., Lu, L. S., & Hung, L. M. (2008). Activation of estrogen receptor is crucial for resveratrol-stimulating muscular glucose uptake via both insulin-dependent and -independent pathways. *Diabetes*, 57(7), 1814–1823.
- Docherty, J. J., Sweet, T. J., Bailey, E., Faith, S. A., & Booth, T. (2006). Resveratrol inhibition of varicella-zoster virus replication in vitro. *Antiviral Research*, 72(3), 171–177.
- Donath, M. Y., & Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. *Nature Reviews. Immunology*, 11(2), 98–107.
- Eeles, E. M. P., White, S. V., O'Mahony, S. M., Bayer, A. J., & Hubbard, R. E. (2012). The impact of frailty and delirium on mortality in older inpatients. *Age and Ageing*, 41(3), 412–416.
- Ettington, M. K. (2010). *Physical immortality: a history and how to guide*. The United States of America: Self Published.
- Fahlbusch, E., Vischer, L., Lochman, J. M., Mbiti, J. S., & Pelikan, J. (1998). *The encyclopedia of Christianity*. Michigan: Wm. B. Eerdmans Publishing Company.
- Fasth, A. E., Bjorkstrom, N. K., Anthoni, M., Malmberg, K. J., & Malmstrom, V. (2010). Activating NK-cell receptors co-stimulate CD4(+)CD28(-) T cells in patients with rheumatoid arthritis. *European Journal of Immunology*, 40(2), 378–387.
- Fedarko, N. S. (2011). The biology of aging and frailty. *Clinics in Geriatric Medicine*, 27(1), 27–37.
- Fontana, L., Meyer, T. E., Klein, S., & Holloszy, J. O. (2004). Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 101(17), 6659–6663.
- Fort, A. T. (2011). State of the art in anti-aging trends. *Clinics in Geriatric Medicine*, 27(4), 507–522.
- Franceschi, C., Monti, D., Scarfi, M. R., Zeni, O., Temperani, P., Emilia, G., et al. (1992). Genomic instability and aging. Studies in centenarians (successful aging) and in patients with Down's syndrome (accelerated aging). *Annals of the New York Academy of Sciences*, 663, 4–16.
- Freund, A., Orjalo, A. V., Desprez, P. Y., & Campisi, J. (2010). Inflammatory networks during cellular senescence: causes and consequences. *Trends in Molecular Medicine*, 16(5), 238–246.
- Fried, L. P., Xue, Q. L., Cappola, A. R., Ferrucci, L., Chaves, P., Varadhan, R., et al. (2009). Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 64(10), 1049–1057.
- Genilli, M., Mazoit, J. X., Bouaziz, H., Fletcher, D., Casper, R. F., Benhamou, D., et al. (2001). Resveratrol decreases hyperalgesia induced by carrageenan in the rat hind paw. *Life Sciences*, 68(11), 1317–1321.
- Haanen, C., & Vermes, I. (1996). Apoptosis: programmed cell death in fetal development. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 64(1), 129–133.
- Hansson, G. K., & Libby, P. (2006). The immune response in atherosclerosis: a double-edged sword. *Nature Reviews. Immunology*, 6(7), 508–519.
- Harman, D. (1956). Aging: a theory based on free radical and radiation chemistry. *Journal of Gerontology*, 11(3), 298–300.
- Hayflick, L., & Moorhead, P. S. (1961). The serial cultivation of human diploid cell strains. *Experimental Cell Research*, 25, 585–621.
- Herold, K., Moser, B., Chen, Y., Zeng, S., Yan, S. F., Ramasamy, R., et al. (2007). Receptor for advanced glycation end products (RAGE) in a dash to the rescue: inflammatory signals gone awry in the primal response to stress. *Journal of Leukocyte Biology*, 82(2), 204–212.
- Hohensinner, P. J., Goronzy, J. J., & Weyand, C. M. (2011). Telomere dysfunction, autoimmunity and aging. *Ageing Dis*, 2(6), 524–537.

- Howitz, K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W., Lavu, S., Wood, J. G., et al. (2003). Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, *425*(6954), 191–196.
- Hung, L. M., Chen, J. K., Huang, S. S., Lee, R. S., & Su, M. J. (2000). Cardioprotective effect of resveratrol, a natural antioxidant derived from grapes. *Cardiovascular Research*, *47*(3), 549–555.
- Johnson, T. E. (2006). Recent results: biomarkers of aging. *Experimental Gerontology*, *41*(12), 1243–1246.
- Karuppagounder, S. S., Pinto, J. T., Xu, H., Chen, H. L., Beal, M. F., & Gibson, G. E. (2009). Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. *Neurochemistry International*, *54*(2), 111–118.
- Kirkwood, T. B., & Austad, S. N. (2000). Why do we age? *Nature*, *408*(6809), 233–238.
- Kuilman, T., Michaloglou, C., Mooi, W. J., & Peepers, D. S. (2010). The essence of senescence. *Genes & Development*, *24*(22), 2463–2479.
- Landenmark, H. K., Forgan, D. H., & Cockell, C. S. (2015). An estimate of the Total DNA in the biosphere. *PLoS Biology*. doi:10.1371/journal.pbio.1002168.
- Leicester, H. M. (1971). *The historical background of chemistry*. New York, NY: Dover Publications Inc..
- Leone, S., Cometta, T., Basso, E., & Cozzi, R. (2010). Resveratrol induces DNA double-strand breaks through human topoisomerase II interaction. *Cancer Letters*, *295*(2), 167–172.
- Lipsitz, L. A. (2002). Dynamics of stability: the physiologic basis of functional health and frailty. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *57*(3), B115–B125.
- Liuzzo, G., Goronzy, J. J., Yang, H., Kopecky, S. L., Holmes, D. R., Frye, F. R., et al. (2000). Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. *Circulation*, *101*(25), 2883–2888.
- Lloyd, D., Aon, M. A., & Cortassa, S. (2001). Why homeodynamics, not homeostasis? *Scientific World Journal*, *1*, 133–145.
- Minamino, T., Orimo, M., Shimizu, I., Kunieda, T., Yokoyama, M., Ito, T., et al. (2009). A crucial role for adipose tissue p53 in the regulation of insulin resistance. *Nature Medicine*, *15*(9), 1082–1087.
- Miyoshi, N., Oubrahim, H., Chock, P. B., & Stadtman, E. R. (2006). Age-dependent cell death and the role of ATP in hydrogen peroxide-induced apoptosis and necrosis. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(6), 1727–1731.
- Mondello, C., & Scovassi, A. I. (2010). Apoptosis: a way to maintain healthy individuals. *Sub-Cellular Biochemistry*, *50*, 307–323.
- Muradian, K., & Schachtschabel, D. O. (2001). The role of apoptosis in aging and age-related disease: update. *Z Für Gerontol Geriatr*, *34*(6), 441–446.
- Neeper, M., Schmidt, A. M., Brett, J., Yan, S. D., Wang, F., Pan, Y. C., et al. (1992). Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. *The Journal of Biological Chemistry*, *267*(21), 14998–15004.
- Ohtani, N., Yamakoshi, K., Takahashi, A., & Hara, E. (2004). The p16INK4a-RB pathway: molecular link between cellular senescence and tumor suppression. *The Journal of Medical Investigation*, *51*(3–4), 146–153.
- Olshansky, S. J., Carnes, B. A., & Cassel, C. (1990). In search of methuselah: estimating the upper limits to human longevity. *Science*, *250*(4981), 634–640.
- Orlova, V. V., Choi, E. Y., Xie, C., Chavakis, E., Bierhaus, A., Ihanus, E., et al. (2007). A novel pathway of HMGB1-mediated inflammatory cell recruitment that requires Mac-1-integrin. *The EMBO Journal*, *26*(4), 1129–1139.
- Park, J. S., Svetkauskaite, D., He, Q., Kim, J. Y., Strassheim, D., Ishizaka, A., et al. (2004). Involvement of toll-like receptors 2 and 4 in cellular activation by high mobility group box 1 protein. *The Journal of Biological Chemistry*, *279*(9), 7370–7377.
- Park, J. S., Gamboni-Robertson, F., He, Q., Svetkauskaite, D., Kim, J. Y., Strassheim, D., et al. (2006). High mobility group box 1 protein interacts with multiple toll-like receptors. *American Journal of Physiology. Cell Physiology*, *290*(3), C917–C924.
- Phillips, D. R., & Kinsella, K. (2005). Global aging: the challenge of success. *Wash Popul Ref Bur Popul Bull*, *60*(6), 5–42.
- Richter, C., Schweizer, M., Cossarizza, A., & Franceschi, C. (1996). Control of apoptosis by the cellular ATP level. *FEBS Letters*, *378*(2), 107–110.
- Ruiz-Mirazo, K., Peretó, J., & Moreno, A. (2004). A universal definition of life: autonomy and open-ended evolution. *B Biosph Orig Life Evol*, *34*(3), 323–346.

- Satoh, A., Brace, C. S., Ben-Josef, G., West, T., Wozniak, D. F., Holtzman, D. M., et al. (2010). SIRT1 promotes the central adaptive response to diet restriction through activation of the dorsomedial and lateral nuclei of the hypothalamus. *Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 30(30), 10220–10232.
- Stanfel, M. N., Shamieh, L. S., Kaerberlein, M., & Kennedy, B. K. (2009). The TOR pathway comes of age. *Biochimica et Biophysica Acta*, 1790(10), 1067–1074.
- Stewart, T. M., Bhapkar, M., Das, S., Galan, K., Martin, C. K., McAdams, L., et al. (2013). Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy Phase 2 (CALERIE Phase 2) screening and recruitment: methods and results. *Contemporary Clinical Trials*, 34(1), 10–20.
- Tchkonia, T., Zhu, Y., van Deursen, J., Campisi, J., & Kirkland, J. L. (2013). Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *The Journal of Clinical Investigation*, 123(3), 966–972.
- Valenzano, DR., Terzibasi, E., Genade, T., Cattaneo, A., Domenici, L., Cellerino, A. (2006). Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate, 16 (3), 296–300
- Vlassara, H. (2005). Advanced glycation in health and disease: role of the modern environment. *Annals of the New York Academy of Sciences*, 1043, 452–460.
- Wallace, D. C. (2005). A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annual Review of Genetics*, 39, 359–407.
- Wang, M., Zhang, J., Jiang, L. Q., Spinetti, G., Pintus, G., Monticone, R., et al. (2007). Proinflammatory profile within the grossly normal aged human aortic wall. *Hypertension*, 50(1), 219–227.
- Weng, N. P., Akbar, A., & Goronzy, J. (2009). CD28(–) T cells: their role in the age-associated decline of immune function. *Trends in Immunology*, 30(7), 306–312.
- Weyand, C. M., Fulbright, J. W., & Goronzy, J. J. (2003). Immunosenescence, autoimmunity, and rheumatoid arthritis. *Experimental Gerontology*, 38(8), 833–841.
- Winder, W. W., & Hardie, D. G. (1999). AMP-activated protein kinase, a metabolic master switch: possible roles in type 2 diabetes. *The American Journal of Physiology*, 277(1 Pt 1), E1–10.
- Witte, A. V., Fobker, M., Gellner, R., Knecht, S., & Flöel, A. (2009). Caloric restriction improves memory in elderly humans. *Proceedings of the National Academy of Sciences of the United States of America*, 106(4), 1255–1260.

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