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Molecular Biomarkers of Aging

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1. Introduction

In the Western World, the public perception of advanced aging involves the inability to survive due to chronic diseases and the combined loss of mobility, sensory functions, and cognition with an exponential growth of health costs. Therefore, biomarkers of human aging are urgently needed to assess the health state of elderly and the possible therapeutic interventions. Aging is considered a process that changes the performances of most physiological systems and increases susceptibility to diseases and death. The aging phenotype is a complex interaction of stochastic, environmental, genetic and epigenetic variables. However, these variables do not create the aging phenotype but favour the loss of molecular fidelity and therefore as the random accumulation of damages in the human organism's cells, tissues, or whole organism during life increases, the probability of disease and death also augments in proportion (Candore et al., 2008). What a biomarker for aging should be or predict is quite broadly defined. A biomarker should not only (i) reflect some basic property of aging, but also (ii) be reproducible in cross-species comparison, (iii) change independently of the passage of chronological time (so that the biomarker indicates biological rather than chronological age), (iv) be obtainable by non invasive means, and (v) be measurable during a short interval of life span. A biomarker should reflect the underlying aging process rather than disease (Warner et al., 2004). In addition, a set of biomarkers should be based on mechanisms described by major theories of aging. A sustained number of biomarkers are currently under investigation, such as inflammatory markers, markers of oxidative stress or markers of telomere shortening but the definition of biomarker is strictly related to the understanding of the mechanisms of aging and we might not be able to define an ideal biomarker yet. Moreover, the biomarkers of aging discussed in literature, are associated not only to age but also to diseases Accordingly, it is crucial to monitor basic mechanisms that underlies the aging process. Noteworthy, a recent study reported that biomarkers of cardiovascular diseases (CVD) and diabetes are useful predictors of healthy aging (Crimmins et al., 2008).

Another problem, which is probably even more challenging, is to understand if a biomarker validated for rodents could be applied equally to humans.

Notably, it should be highlighted that mammalian cells have developed highly refined inducible systems against a variety of stressful conditions; upon stimulation, each one of these systems can be engaged concertedly to alleviate and hinder the manifestation of a distinctive age-related disorder. In this context, increasing scientific evidence supports a pivotal role for the heat shock proteins in the protection against oxidative stress and inflammation. Heat shock response is a fundamental cellular survival pathway, involving both transcriptional and post-transcriptional regulation. The impairment of this regulatory mechanism might directly contribute to the defective cellular stress response to oxidative stress and deregulation of inflammatory processes, which characterizes senescence.

In the present chapter, we will focus on the importance of biomarkers involved in inflammatory responses, oxidative stress but also markers based on immunosenescence. Additionally, we will describe the major experimental methods that are available in biogerontology for the interpretation of the aging phenotypes. In summary, we will present an overview on the current knowledge of the complex molecular and biological events leading to cellular senescence and how we can measure this progression to possibly improve our quality of life.

2. Aging and the immune system

Aging is accompanied by a general dysregulation in immune system function, commonly referred to as immunosenescence. This progressive deterioration affects both innate and adaptive immunity, although accumulating evidence indicates that the adaptive arm of the immune system may exhibit more profound changes. Most of our current understanding of immune senescence stems from clinical and rodent studies. Studies have suggested that aging is associated with increase permeability of mucosal barriers, decreased phagocytic activity of macrophages and dendritic cells (DCs), reduced natural killer (NK) cell cytotoxicity, and dysregulated production of soluble mediators such as cytokines and chemokines (Weiskopf et al., 2009). These alterations could lead to increased pathogen invasion and poor activation of the adaptive immune response mediated by T and B-lymphocytes. The age-related changes which occur in the adaptive and innate immune response are summarized in Table 1.

Aging, is also associated with quantitative and qualitative changes within the naive CD4+T-cell compartment (Aspinall & Andrew, 2000; Fulop et al., 2006; Kilpatrick et al., 2008). Decreased numbers of recent thymic emigrants (RTE), shortened telomeres, hyporesponsiveness to stimulation, decreased proliferative capacity, reduced IL-2 production, alterations in signal transduction and changes in cell surface phenotype (Whisler et al, 1996; Fulop et al., 2006; Kilpatrick et al., 2008) have all been reported. These changes likely contribute to the poor response to vaccines and increased susceptibility to infectious diseases and neoplasms reported for older adults (Webster, 2000; Effros, 2000; Herndler-Brandstetter et al., 2006).

Aging causes a shift in the ratio of naive to memory T-cells, with associated changes in the cytokine profile that favor increases in pro-inflammatory interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interferon γ (IFN γ), tumor necrosis factor (TNF α), and transforming growth factor

(TGF β) (Sanson et al., 2008). The production of IL-6, but not IL-1 β or TNF- α , by peripheral blood mononuclear cells increases in the elderly (Roubenoff et al., 1998), and IL-1 β production increases in peripheral blood mononuclear cells in older animals (Chung et al., 2006). In contrast, IL-1 β levels are higher and IL-6 levels lower in the livers of old rats than young rats (Rikans et al., 1999).

As the hematopoietic system ages, the immune function deteriorates, the lymphoid potential diminishes, and the incidence of myeloid leukemia increases (Rossi et al., 2005). Aging leads to increased stem cell dysfunction, and as a result leukemia can develop in failed attempts by the bone marrow to return to a homeostatic condition after stress or injury. Stem cells leave the hibernation state and undergo self-renewal and expansion to prevent premature hematopoietic stem cell (HSC) exhaustion under conditions of hematopoietic stress (Walkey et al., 2005). HSCs in older mice produce a decreased number of progenitors per cell, decreased self-renewal and increased apoptosis with stress (Janzen et al., 2006).

The remaining stem cells divided more rapidly as if to compensate for those that were lost. Stimulating old stem cells to grow more rapidly, perhaps by stress such as infrared (IR), puts stem cells at greater risk of becoming cancer cells because of acquired DNA damage.

Metabolically active senescent cells, identified by the biomarkers of cellular aging, such as the γ -H2AX foci and perhaps the senescence-associated β -galactosidase (SA- β -gal) enzyme, accumulate in aging primates (Herbig et al., 2006). Cellular senescence can be induced in one of two ways. Firstly, reactive oxygen species (ROS) may contribute to the plentiful single-strand breaks (SSBs) and double-strand breaks (DSBs) present in senescent cells (Sedelnikova et al., 2004); this is a form of telomere-independent stress-induced senescence. Alternatively, telomere-dependent uncapping of telomere DNA causes replicative senescence. An increase in oxidative stress is a more probable cause of HSC senescence than telomere erosion (Beauséjour et al., 2007). High doses of IR lead to apoptosis of HSCs, while lower doses cause HSCs to senesce and lose the ability to clone themselves (Wang et al., 2006). Furthermore, irradiated normal human fibroblasts and tumor cell lines can also lose their clonogenic potential and undergo accelerated senescence (Mirzayans et al., 2005). The inhibition of tumorigenesis by cellular senescence is oncogene-induced and linked to increased expression of tumor suppressor genes cyclin-dependent kinase inhibitor 2A (*p16INK4a* or *CDKN2A*) and tumor protein 53 (*TP53*) via the DNA damage response (Bartkova et al., 2006). Recent research points to the p16INK4a protein being an important aging biomarker as its concentrations in peripheral blood exponentially increase with chronological age, reducing stem cell self-renewal (Liu et al., 2009). The few articles published to date linking radiation's health effects and p16INK4a can be paradoxical with regard to aging. A Chinese study showed the cumulative radiation dose of radon gas among uranium miners to be positively associated with the aberrant promoter methylation and inactivation of the *p16INK4a* and *O6-methylguanine-DNA methyltransferase* (MGMT) genes in sputum, perhaps indicating the early DNA damage and a greater susceptibility to lung cancer (Su et al., 2006).

The number and proliferation potential of stem cell populations, including those of the intestinal crypt and muscle, decrease with age, leading to a progressive deterioration of tissue and organ maintenance and function (Schultz et al., 1982; Martin et al., 1998). Macromolecular damage in general and DNA damage in particular, accumulate in HSCs with age (Rossi et al., 2007). The reduced ability to repair DNA DSBs leads to a progressive

loss of HSCs and bone marrow cellularity during aging (Nijnik et al., 2007). In addition, high radiation dose (>12.5 Gy) from ⁴⁵Ca, a bone-targeting beta-ray emitter (Barranco et al., 1969), resulted in marked reduction in marrow cellularity, similar to the one observed in normal aging indicating a possible contribution of the DNA-repair mechanisms to the aging process.

	IMMUNE BIOMARKERS	AGE-RELATED INCREASE	AGE-RELATED DECREASE
INNATE IMMUNE SYSTEM	Cytokines and Chemokines	Serum levels of IL6, IL1β and TNFα	
	NK cells	Total number of cells	Proliferative response
	Dendritic cells		Capacity to stimulate antigen specific T-cells
	Neutrophils		Bactericidal activity; Oxidative burst
	Macrophages		Phagocytic capacity
ADAPTIVE IMMUNE SYSTEM	T-lymphocytes	Release of proinflammatory cytokines	Number of naive T-cells; Diversity of the T-cell repertoire
	B-lymphocytes	Autoreactive serum antibodies	Number of naive B-cells; Antibody affinity; Generation of B-cell precursors

Table 1. Age-related changes in the innate and adaptive immune system.

3. Oxidative stress and inflammation as causes of aging

To date, there are several theories which attempt to explain the process of aging, such as telomere theory, caloric restriction, and evolutionary theory. The oxidative stress hypothesis/free radical theory of aging, updated by Harman in 2006 (Harman, 2006) offers a possible biological explanation of the entire aging process. In a biological context, a condition of oxidative stress occurs when there is an imbalance between oxidant molecules and antioxidant defensive molecules. Such critical balance is disrupted when antioxidants are depleted or if the formation of ROS increases beyond the ability of the antioxidative systems. Additionally, the free radical theory proposed that the production of intracellular ROS is the major determinant of life span.

However, the most critical problem is to find a correlation between oxidative biomarkers amounts and human health. Nevertheless, according to the free radical theory of aging, oxidative stress increases with increasing age resulting in oxidative DNA damage, protein oxidation and lipid peroxidation.

One of major risk markers of oxidative damage of nucleic acids is the 8-hydroxy-29-deoxyguanosine (8-OHdG). So far, 8-OHdG is the most studied oxidative DNA lesion and it is formed when ROS act on deoxyguanine in DNA (Ravanat et al., 2000). 8-OHdG can alter

gene expression, inhibits methylation and its mutagenic potential leads to GC → AT conversion. The formation of 8-OHdG in leukocyte DNA and the excretion of 8-OHdG into urine have been frequently measured to assess oxidative stress in humans. However, even though interesting results have been obtained with 8-OHdG, several studies have associated aging with a progressive loss of antioxidant defence.

Recently, several findings have emphasized the importance of lipid peroxidation in relation to the role of caloric restriction and the extension of longevity (Sanz et al., 2006). Lipid peroxidation products have also been shown to be mutagenic and carcinogenic and has been implicated as the underlying mechanisms in numerous disorders including aging. Notably, lipid oxidation not only causes membrane disruption but also produces aldehydic species, such as malondialdehyde (MDA), able to perpetrate further damage by binding to and modifying proteins. Although producing contradictory results, the measure of lipid peroxidation is an example of biomarkers of oxidative stress. The measurement of MDA is very easy to perform, fast and not expensive. MDA is often utilized to evaluate human aging and in numerous studies MDA was significantly higher in healthy elderly, confirming the presence of increased lipoperoxidation in old age.

Another important product generated by lipid peroxidation is 4-hydroxy-2-nonenal (HNE) that reacts with nucleic acids, proteins, and phospholipids inducing many cytotoxic, mutagenic, and genotoxic effects (Uchida, 2003). Low-density lipoproteins (LDL) seems to be another good marker because oxidised LDL appears to be involved in the development of various pathological conditions aging related. Measurements of LDL could be obtained *in vivo* by measuring oxidised LDL particles in blood using immunological methods with appropriate specificity.

In addition, phosphatidylcholine hydroperoxides (PCOOH) measured in blood or tissue is also an acceptable marker of lipid peroxidation.

Recently, isoprostanes (IsoPs), compounds that are produced *in vivo* by free radical-induced peroxidation of arachidonic acid, have been also proposed to assess the oxidative stress status but we have only few experimental evidence and convincing outcomes have not emerged yet (Montuschi et al., 2007). Particularly, the analysis of F2-isoprostanes has revealed a role for free radicals and oxidant injury in a wide variety of human diseases. However, it must be taking into account that the measurement of F2-isoprostanes represents a snapshot of oxidant stress at a discrete point in time. Indeed, F2-isoprostanes are cleared rapidly from the circulation. However, such molecules that are stable isomers of prostaglandin F2, seems to be the best reliable marker and it has been proposed as most affidable index of systemic or “whole body” oxidative stress over time.

Closely related to oxidative stress is the protein oxidation. The main molecular characteristic of aging is the progressive accumulation of damages in macromolecules and age related damage in proteins have been reported in cells, tissues and organs (Rattan, 2006). The measurement of the protein oxidation is a clinically important factor for the prediction of the aging process and age-related diseases. The most widely studied oxidative stress-induced modification to proteins is the formation of carbonyl derivatives. Carbonyl formation can occur through a variety of mechanisms including direct oxidation of certain amino-acid side chains and oxidation-induced peptide cleavage. Furthermore, advanced oxidation protein products considered as biomarkers to estimate the degree of oxidative modifications of

proteins and carbonyl groups may be introduced into proteins by reactions with aldehydes, reactive carbonyl derivatives or through their oxidation products with lysine residues of proteins. Although all organs and all proteins can potentially be modified by oxidative stress, certain tissues and specific protein may be especially sensitive. For instance, recent studies characterized oxidatively modified proteins in the brain and identified specific proteins that are oxidatively modified in Alzheimer's disease (Butterfield & Sultana, 2007).

Aging is accompanied by chronic low-grade inflammation status and inflammatory mediators may be useful to monitor aging processes. Molecular activation of pro-inflammatory genes by altered redox signaling pathways will eventually lead to inflamed tissues and organs. Accordingly, molecular inflammation is an important biological component of aging. In this perspective, nuclear factor of kappa light polypeptide gene enhancer in B-cells (NF- κ B) is a transcription factor that plays a pivotal role in modulating cellular signaling of oxidative stress-induced molecular inflammation. For example, stimulus-mediated phosphorylation and the subsequent proteolytic degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (I κ B) allows the release and nuclear translocation of NF- κ B, where it transactivates several target genes such as forkhead box (FOXO), IL-1 β , IL-6, TNF α , adhesion molecules, cyclooxygenase-2 (COX-2) and nitric oxide synthases inducible (iNOS), all key players in inflammation.

Aging is associated with activation of both the innate and the adaptive immune system. As mentioned above, during aging increased blood levels of proinflammatory cytokines such as IL-6 and TNF α can be observed. In healthy elderly populations, high circulating levels of TNF α and IL-6 predict mortality, in a manner independent from comorbidity (Bruunsgaard & Pedersen, 2003).

Additionally, an inflammatory response appears to be the prevalent triggering mechanism driving tissue damage associated with different age-related diseases and the definition of "inflamm-aging" has been coined to explain the underlining inflammatory changes common to most age-associated diseases (Licastro et al. 2005).

Finally, reduced glutathione (GSH) is a major intracellular non-protein -SH compound and is accepted as the most important intracellular hydrophilic antioxidant (Melov, 2002). Glutathione system is the most important endogenous defense system against oxidative stress in body. Under oxidative conditions GSH is reversibly oxidized to glutathione disulfide (GSSG). A recent study on age-related changes in GSH in rat brain suggests a significant age-related reduction in the GSH level in all regions of the brain, associated with an increase in GSH oxidation to GSSG and decrease in the GSH/GSSG ratio (Zhu et al., 2006).

4. Methods for analysis of biological aging

The aging research requires multi- and transdisciplinary approaches and new high-throughput technologies are continually in development, increasing exponentially the amount of biological informations in aging research and elucidating complex unknown mechanisms. Although there have been extraordinary advances in study related to gene expression, proteomic and functional data, one challenge in aging research is to bring together this large variety of data that are still fragmented. Here, we provide a brief description of the main technological approaches for biomarkers discovery and for

analyzing the molecular and cellular changes involved in aging cells. We also describe the major databases, computational tools and bioinformatics methods that are available in biogerontology for data interpretation of the aging phenotypes.

Analysis of gene-expression data has led to remarkable progress in many biomedical disciplines, including gerontology. Numerous methods have been developed for this analysis, but the emergence of high-throughput expression profiling and sequencing, such as microarray technology (Blalock et al., 2003) or more recently next-generation sequencing RNA-Seq have become diffusely used leading to breakthroughs in the investigations of aging (Twine et al., 2011). The application of microarray technology to gerontological studies has improved our understanding of mechanisms of aging (Golden & Melov, 2007) allowing to elucidate molecular differences associated with aging and to scan the entire genome for genes that change expression with age. The core principle of a microarray experiment is the hybridization of RNA/DNA strands of at least two different conditions, such as normal and disease or different ages, with a microarray chip. Briefly, the data collection is followed by bioinformatics analysis that require background noise subtraction, normalization and identification of statistically significant changes with dedicated software packages that calculate through multiple statistical measurements the significance for each gene. Ultimately, an application of transcriptomic microarray reported the first assessment of age-related alterations in gene expression in a large population-based cohort suggesting that modification of messenger RNA (mRNA) processing may comprise an important feature of human aging (Harries et al., 2011). In addition, an example of differential expression analysis in aging is the comparison of Ames dwarf mice *Prop1^{df/df}* versus *Prop1^{+/+}* and Little mice *Ghrhr^{lit/lit}* versus *Ghrhr^{+/lit}* (Amador-Noguez et al., 2004). In both cases, the mutants show delayed aging with significantly increased lifespan and the authors found 1125 and 1152 differentially expressed genes in these mutants, respectively, using analysis of variance (ANOVA). There is a growing number of age-related molecular repositories and one database of gene expression profiles during aging is the Gene Aging Nexus, which features a compilation of aging microarray data and microarray datasets across different platforms and species (<http://gan.usc.edu/>) (Pan et al., 2007).

The genomic convergence approach is a new powerful method alternative to genome-wide association studies that combines transcriptional profiling, expression of quantitative trait mapping and gene association. Briefly, microarray technology are used to identify genes that show age-related changes in expression. In the next step single nucleotide polymorphisms (SNPs) are tested for association with the expression of age-regulated genes and finally the expression of quantitative trait loci (eQTLs) are tested for association with a phenotype of aging (Wheeler et al., 2009).

Currently, basic methods to understand biological processes and to identify possible candidate biomarkers for a specific pathology are shifted toward “omics” approaches, where all classes of biological compounds can be analyzed by respective “omic” techniques. To date, proteomic investigations have special relevance to aging-related research since altered protein interactions may have a key role in aging-related diseases. Different proteomic technology platforms were applied to define the proteomes and conventional techniques as two-dimensional gel electrophoresis (2DE), surface-enhanced laser desorption/ionization (SELDI), liquid chromatography-mass spectrometry (LC-MS), capillary electrophoresis (CE) coupled to mass spectrometry (CE-MS) and protein arrays are

also associated to aging related studies. The proteomic analysis require adequate tools for data analysis and there are several bioinformatic approaches in proteomics. Many algorithms have now been designed to handle the increasing amount of data that are available thanks to proteomic analysis and numerous computational approaches and software tools have been developed to automatically assign candidate peptide sequences to fragment ion spectra, for example, SEQUEST, MASCOT or ProteinProspector. In addition, quantitative proteomics based on stable isotope labeling, such as isotope-coded affinity tags (ICAT) or stable isotope labeling by amino acids in cell culture (SILAC) represents a promising approach for aging studies providing important information to interpret protein biomarkers of age-related disease (Zhang et al., 2005). The investigation of changes in metabolite fluxes or the analysis of all metabolites in high-throughput fashion, called metabolomics (or metabonomics), is an attractive and expanding field in aging research. One goal of the metabolomics is to assess the impact of metabolite concentrations on aging phenotype. Several studies have emerged with metabolomics approach traditionally using nuclear magnetic resonance (NMR) and recently MS techniques. An example of the application of MS-based metabolomics in aging research is given by Lawton et al. which analyzed the plasma of 269 individuals and discovered that age significantly altered the concentrations of over 100 metabolites (Lawton et al., 2008).

In addition, there are available for metabolomics researchers interested in aging databases for metabolite identification, such as METLIN that contains information on metabolites, as well as MS data (<http://metlin.scripps.edu/>) or The Human Metabolome Database (<http://www.hmdb.ca/>) with information on small molecule human metabolites.

Taking into account that the human aging phenotype is a highly polygenic trait which involves changes in genes involved in multiple processes and results from a combination of different factors, systems biology approach is particularly powerful in studies of aging. To date it seems to be the only method able to define and connect the large volumes of experimental data generated by “omics” fields. The final aim of the systems biology of aging is to generate an integrative approach which elucidates the molecular mechanisms of aging and to characterize this phenotype at systemic/organism level. In addition to quantify and integrate data produced by high-throughput technologies, the systems biology approach combines data-driven modelling and hypothesis-driven experimental studies in order to link aging phenotypes and its causes. One area in which systems biology can be applied to aging research is the generation of a conceptual whole cell model that considers the dynamic behaviors of cellular metabolism. The whole cell representation is structured into subcellular entities not only connected by protein-protein interactions but also by process related to metabolism, oxidative stress or transcriptional regulation. The goal of aging cell modelling is to build a conceptual framework through the simulation of dynamic system and to make predictions about the aging phenotype. The systems biology community has developed tools and modeling platforms to facilitate the representation of metabolic and signaling pathways among biological processes and allowing the understanding of complex phenomena such as aging. Systems Biology Markup Language (SBML) is the main language for coding biological models and currently there are two softwares that support construction of models in SBML, CellDesigner and JDesigner (Oda et al., 2005). Recently, by using SBML, McAuley et al. generated an *in silico* brain aging model which may help to predict aging-related brain changes in older people (McAuley et al., 2009). Most of genes and proteins exert their functions within a complex network of interactions and another applications of systems biology is the assemblage of interactomes. The building of interaction

networks allow to define changes in interaction of proteins implicated in aging process that are involved in maintaining the integrity of the human genome. In the protein-protein interaction (PPI) networks, each protein is a node and each interaction an edge and the first attempt towards constructing a “human longevity network” via analysis of human PPIs was made by Budovsky et al. in 2007 (Budovsky et al., 2007). According to the BioGrid database, the authors constructed a “core longevity network” that comprises 153 longevity-associated proteins and 33 non-longevity-associated proteins that have connections with at least five longevity-associated proteins or more. Therefore, network-based approaches are notably valuable for deciphering complex biological systems providing insights about aging, longevity and age-related disease. In addition, there are several collections of online resources available for biogerontologists that can also serve for the visualization of protein-protein interactions. Databases focused on genes related to aging and/or longevity include GeneAge and AnAge featured by the Human Aging Genomic Resources (<http://genomics.senescence.info/>) that is a collection of databases and tools designed for understanding the genetics of human aging. GeneAge is a curated reference database of different searchable data sets of genes associated with the human aging phenotype. One possible approach of GeneAge is the visualiztion of protein-protein interactions with one or more genes as query but additional ways can be used to build genes and protein interaction networks in conjunction with data stored in interaction databases such as IntAct (Kerrien et al., 2007). There is an expanding number of age-related repositories, such as NetAge (<http://netage-project.org/>) which provides information on microRNA-regulated protein-protein interaction networks that are involved in aging and related processes. Furthermore, one gene expression database is AGEMAP (Zahn et al., 2007), which allows to analyze multiple genes and mechanisms affect aging describing changes in expression levels in different mouse tissues. Finally, one database on human aging which will be available to the public is MARK-AGE (<http://www.mark-age.eu/>), a large-scale integrated project supported by the European Community. The aim of this project is to conduct a population study in order to identify a set o biomarkers of aging.

The coordinate assessment of genotypes, trascriptional and proteomic profiles in association with system and computational biology strategies will be able to reach a comprehensive model for the study of human aging and longevity but also for healthy aging.

5. Conclusion

Biomarkers of aging are an hot topic and have the ability to improve our life. Various parameters are directly affected and altered during aging and several indicators are being used to evaluate the aging process. However, not all can be used as biomarker of aging because many of them are influenced by different factors such as diet, enviroment or type of tissue. In addition, some biomarkers are dependent by the methods used to measure them. Accordingly, there is not yet a “pure” biomarkers of aging and the markers discussed are related not only to age but also to disease.

Furthermore, it is a subject of debate whether the determination of biological age markers is really addressing aging itself, or if it indicates stress induced acceleration of the age process by exogenic factors.

Aging is a multi-dimensional process and these biomarkers could be used to monitor and identify the development of age-associated disease providing new anti-aging strategies.

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7. Abbreviations

The abbreviations used are: CVD, cardiovascular diseases; DCs, dendritic cells; NK, natural killer; RTE, thymic emigrants; IL-1 β , Interleukin-1 β ; IL-6, Interleukin-6; IFN γ , interferon γ ; TNF α , tumor necrosis factor α ; HSC, hematopoietic stem cell; SA- β -gal, Senescence-Associated β -galactosidase; ROS, reactive oxygen species; SSBs, single-strand breaks; DSBs, double-strand breaks; IR, infrared; *p16INK4a* or CDKN2A, cyclin-dependent kinase inhibitor 2A; TP53, tumor protein 53;MGMT,O6-methylguanine-DNAmethyltransferase;8-OHdG,8-hydroxy-29 deoxyguanosine; MDA, malondialdehyde; HNE, 4-hydroxy-2-nonenal; LDL, low-density lipoproteins; PCOOH, phosphatidylcholine hydroperoxides; IsoPs, isoprostanes; NF-k β , nuclear factor of kappa light polypeptide gene enhancer in B-cells; Ik β , nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; FOXO, forkhead box; COX-2, cyclooxygenase-2; GSH, reduced glutathione; GSSG, glutathione disulfide; mRNA, messenger RNA; SNPs, single nucleotide polymorphisms; eQTLs, expression of quantitative trait loci; 2DE, two-dimensional gel electrophoresis; SELDI, surface-enhanced laser desorption/ionization; MS, mass spectrometry; LC, liquid chromatography; CE, capillary electrophoresis; NMR, nuclear magnetic resonance; SBML, Systems Biology Markup Language; PPI, protein-protein interaction.

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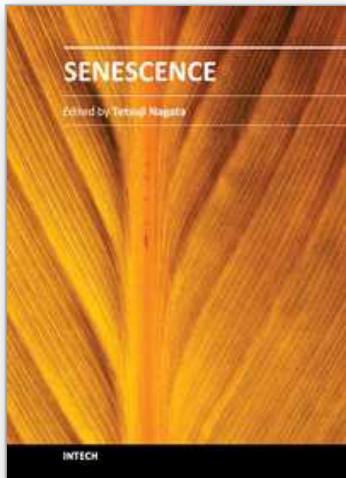
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