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Review

A Current Genetic and Epigenetic View on Human Aging Mechanisms

Saša Ostojić, Nina Pereza and Miljenko Kapović

Department of Biology and Medical Genetics, School of Medicine, University of Rijeka, Rijeka, Croatia

A B S T R A C T

The process of aging is one of the most complex and intruguing biological phenomenons. Aging is a genetically regulated process in which the organism's maximum lifespan potential is pre-determined, while the rate of aging is influenced by environmental factors and lifestyle. Considering the complexity of mechanisms involved in the regulation of aging process, up to this date there isn't a major, unifying theory which could explain them. As genetic/epigenetic and environmental factors both inevitably influence the aging process, here we present a review on the genetic and epigenetic regulation of the most important molecular and cellular mechanisms involved in the process of aging.

Based on the studies on oxidative stress, metabolism, genome stability, epigenetic modifications and cellular senescence in animal models and humans, we give an overview of key genetic and molecular pathways related to aging. As most of genetic manipulations which influence the aging process also affect reproduction, we discuss aging in humans as a post-reproductive genetically determined process. After the age of reproductive success, aging countinously progresses which clinically coincides with the onset of most chronic diseases, cancers and dementions. As evolution shapes the genomes for reproductive success and not for post-reproductive survival, aging could be defined as a protective mechanism which ensures the preservation and progress of species through the modification, trasnmission and improvement of genetic material.

Key words: *calorie restriction, cellular senescence, epigenetics, genomic instability, insulin/Igf-1 signalling pathway, longevity genes, oxidative stress, reproduction*

Introduction

Over the last century, advances in medicine and biotechnology, as well as increasing life standard have contributed to a rapid growth of the elderly population. This increase in the percentage of the elderly has created many social problems and has become an inevitable healthcare problem.

The process of aging is one of the most complex and intruguing biological phenomenons. Aging is usually defined as the progressive and generalized loss of function resulting in an increasing vulnerability to environmental factors and growing risk of disease and death[1].

Although aging is a widespread process and one of the most studied biological processes, little is known about the basic genetic and molecular mechanisms which influence the process itself, especially in humans. Considering the complexity of mechanisms involved in the regulation of aging, up to this date there are more than 300 theories which are trying to explain them, but none of the theories provide complete answers[2]. Theories are usually categorized into »error« and »program« theories[3]. The »error theories« define aging as gradual accumulation of random molecular damage which leads to deterioration of physiological functions, phenotypic changes and increased risk for development of various diseases and death. Oppositely, »program theories« suggest that organisms are programmed to age and live for a genetically pre-determined lenght of time[4]. As the environment and lifestyle constantly influence genetic changes and epigenetic modifications of the genome, the aging theories inevitably overlap at various levels, and it is impossible to assort them into strict categories or analyze one category with the exclusion of others. Due to these facts, aging can be defined as a genetically regulated process in which the organism's maximum lifespan potential is pre-determined while the rate of aging is influenced by environmental factors and lifestyle.

Although aging is under genetic control, it is probably not programmed in the sense that there are »longevity

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genes« or »gerontogenes« which pre-determine the process itself, but rather it is considered that aging is a physiological process which follows embryonic and postnatal development and is the consequence of a constant interaction between the genome and the environment.

Various endogenous and exogenous biological and chemical stresses, cause damage of macromolecules, including DNA, lipids and proteins, which accumulate during time. As a result, there is a constant increase in the vulnerability of the body, leading to a continuously increasing risk of disease and death. Later in life, the balance between damage and repair, which are mainly under genetic control, becomes crucial for the maintenance of health as well as development of diseases and aging.

Much of what we know today about the genetics of aging comes from studies on animal models[5]. The major model systems include yeast *Saccharomyces cerevisiae*, roundworm *Caenorhabditis elegans*, fruit fly *Drosophila melanogaster* and rodent *Mus musculus*. Genetic studies on these models have uncovered numerous genetic pathways which regulate metabolism, oxidative stress and genomic integrity and also influence longevity. These experiments have demonstrated that induced mutations in various genes which make up a molecular pathway can dramatically increase lifespan. Although most of these organisms live much shorter (mice live up to 4 years) and have distinct physiology than humans, the crucial genetic and molecular pathways are evolutionary conserved across species which makes them a useful basis for the research on human aging.

Here we present a review on the genetic and epigenetic regulation of the most important molecular and cellular mechanisms involved in the process of aging based on studies on animal models and humans. As the environment in which organisms live, including humans, has critical importance in genome shaping, and as same genes in different environmental settings lead to different phenotypical effects, we also emphasize the importance of epigenetic modifications in the aging process and discuss the connection between reproductive ability and aging.

Genetic Factors Regulating Aging

Although aging and longevity are genetically regulated, the »longevity genes« haven't been found yet. However, there are several proposed classes of genes which influence aging: »longevity assurance genes« which enhance structure and function of the organism throughout the life span; »antagonistic pleiotropy alleles« which enhance reproductive fitness early in the life span, but have negative effects late in the life span and; »mutation accumulation« which affects gene structure and changes phenotypic expression during time[6]. Aging is most certainly genetically influenced, but because of the complexity of the human genome and the constant interaction between the genome and the environment, it is most likely that there is a polygenic basis for the control of the rate of aging.

Single gene variations in numerous genetic pathways have been shown to enhance life span of model organisms. Experimental manipulation of these pathways is inevitably related to reproductive fitness. For example, manipulations which mimic adverse environmental conditions also downregulate reproductive activity and protect the organism during transient environmental challenges.

1. Oxidative damage

One of the oldest and best studied theories of aging is »the free radical theory« which supposes that aging results from the progressive and irreversible accumulation of molecular damage caused by free radicals. Most biologically relevant free radicals are generated during oxidative metabolism in mitochondrion and are thus, named reactive oxygen species (ROS). Long-term exposure to ROS has deleterious effects on macromolecules including DNA damage, lipid peroxidation and protein damage and is reffered to as oxidative stress[7]. Accumulation of oxidative damage causes dysfunction of organelles, cellular senescence or death and is associated with the development of many age-related diseases[8].

In multicellular organisms different cell types age at a different rate. Post-mitotic cells, such as neurons, cardiac myocytes and skeletal muscle cells are more susceptible to oxidative damage than dividing cells and thus suffer the most remarkable age-related changes, including progressive loss of function and cell death[9].

The degree of oxidative stress to the cell is not only determined by the level of deleterious effects but rather represents the balance between oxidative damage and possibilities of cellular defense. One of these mechanisms includes antioxidantive enzymes, molecules which convert free radicals into energetically stable molecules. There are two kinds of antioxidants – endogenous, which are generated in the organism (superoxide dismutase, catalase, peroxidases) and exogenous (vitamins C and E, β-carotene, coenzyme Q10, selenium)[8].

Genetic regulation of oxidative damage

The rate of aging could be affected by differences in genetically controlled resistance to oxidative stress. Genetic manipulations which increase oxidative damage shorten lifespan, while those which lead to increased resistance to oxidative damage, extend it. The majority of studies on oxidative damage include manipulations of genes encoding for antioxidative enzymes and enzymes involved in mitochondrial oxidative metabolism. As most of these genes are evolutionary conserved across species, studies on animal models might provide insights into how these mechanisms are involved in the regulation of human aging.

These studies have also shown that extension of lifespan as well as premature aging in models from yeast to mice support the association between metabolic rate, oxidative metabolism, stress resistance and aging[10]. This is known as the »rate of living theory« which states that the metabolic rate of a species determines its life expec-

tancy is closely related to the »free radical theory«. Higher metabolic rates often result in shorter lifespan partly due to the increased production of free radicals[11].

C. elegans. Mutational inactivation of several mitochondrial genes, such as the *clk-1* gene which encodes a mitochondrial protein involved in the synthesis of ubiquinone, increases longevity by 15–35% and induces resistance to oxidative stress[12]. This gene is part of the *»clock group of genes«* which are evolutionary conserved in many species and mutations in these genes reduce the rate of metabolism, lead to decreased ROS production and slower accumulation of damage[13]. Also, mutations which impair the expression of genes which encode the subunit of the succinate dehydrogenase and a cytosolic catalase, the *mev-1* and *ctl-1* gene, respectively, reduce lifespan. Mutants with impaired *mev-1* functions also have reduced SOD activity and are hypersensitive to oxygen[14].

D. melanogaster. Overexpression of the *SOD1 (CuZn--SOD), SOD2 (Mn-SOD)* and *cat* genes which encode for copper/zinc and manganese superoxide dismutases and catalase antioxidants, respectively, increases the lifespan of transgenic D.melanogaster by 34% and makes them highly resistant to oxidative stress[15].

Overexpression of the *Methuselah (Mth)* gene encoding the G protein–coupled receptor (GPCR), which is homologous to a mammalian family of peptide hormone receptors, increases longevity of D.melanogaster by 35%. Although its exact function is not known, these animals become resistant to oxidative stress, heat and starvation[16]. Flies with mutations in the *stunted* gene which encodes ligands of *Mth* show increased lifespan and resistance to stress[17].

M. musculus. Certain genetic interventions which extend life expectancy in invertebrates do not have the same effect in mice[18]. Mice knocked out for *glutathione peroxidase (GPX1)* gene do not show signs of rapid aging but develop multiple age-related diseases and die prematurely[19]. Disruption of the mitochondrial form of *superoxide dysmutase 2 (SOD2)* gene is lethal due to neurodegeneration and dilated cardiomyopathy[20,21]. In contrast, overexpression of the catalase and *SOD2* genes increases lifespan[22].

The association between calorie intake, rate of metabolism and the production of ROS has also been observed in mice. Deletion of *Shc* gene encoding the $p66^{shc}$ protein, an important regulator of cellular redox potential and oxidative damage in response to extracellular signals, including insulin, reduces production of ROS, increases resistance to oxidative stress–induced apoptosis, delays aging and increases longevity by 30%[23]. $p66^{Shc}$ knockout mice are also protected against vascular, cardiac, and renal diseases attributable to hypercholesterolemia, diabetes and aging[24].

Humans. The association between genes regulating oxidative stress and human aging has been studied to a much lesser extent than in animal models. The exact role of polymorphisms in genes encoding for antioxidants is not known. Up to this date there are only a few studies which have associated *SOD2* genetic variations with cancer, immunosenescence and DNA damage but not with lifespann[25]. Thus, the exact role of these genetic factors in human longevity remains to be elucidated.

Alterations in the intracellular redox state activates several stress-acting pathways, including phosphatidylinositol-3-OH kinase (PI3K)/Akt**,** ERK (extracellular signal-regulated kinase), cJun, MAPK (mitogen-activated protein kinase), NFkB (nuclear factor kappa B) and p53, which then alter the expression of target genes to provide a pro-survival signal during oxidative stress[26]. These pathways are also involved in the processes of normal growth, metabolism and cell signaling.

It has recently been shown that the Raf/MEK/ERK and PI3K/Akt signalling pathways which are essential for cellular proliferation, are down regulated in the nuclei of senescent cells resulting in decreased cell survival[26].

2. Metabolism and aging

The rate of metabolism and various dietary factors have a profound effect on numerous aspects of health and aging. Calorie restriction (CR) (the diet which contains all essential nutrients but is restricted in calories by 30–40% compared to animals fed *ad libitum*) not only increases longevity but also postpones age-related diseases, such as cardiovascular diseases, diabetes and cancer[27,28]. The maintenance of homeostasis throughout an organism's life span requires constant adaptation to changes in energy levels. The limitation of food intake without malnutrition increases longevity and postpones aging in all tested model organisms[29,30], but the exact mechanism by which CR influences aging is not known. It is supposed that CR reduces metabolic rate, decreases the production of ROS and induces resistance to various forms of stress[11]. Nutritional factors have a profound influence on genetic material and CR alters the level of expression of many genes, regulates transcription factors and modulates epigenetic modifications[31] and genetic interventions in genes involved in signalling pathways which respond to nutrient status have been shown to affect aging and longevity.

Insulin/insulin-like growth factor 1 signalling pathway

Calorie intake and diet are closely related to endocrine system. The insulin/insulin-like growth factor 1 (Ins/Igf-1) is the best characterized signalling pathway which regulates the response to glucose. Organisms with genetic manipulations in Ins/Igf-1 pathway develop a phenotype similar to CR, exhibit changes in glucose metabolism and have significantly extended lifespan[32]. This pathway is conserved in C.elegans, D.melnogaster, M. musculus and humans and regulates the activity of FOXO transcription factors which activate antioxidantive enzymes, heat shock proteins, metabolic genes, protein kinases and many others[33,34]. All of these long-lived mutants show certain similarities, such as low levels of circulating Igf-1, low plasma insulin and glucose levels, increased

tissue sensitivity to insulin, reduced production of ROS and resistance to heat and oxidative stress[35]. As Ins/Igf-1 pathway is involved in the regulation of metabolism, growth and reproduction, genetic interventions which increase lifespan also affect these functions.

C. elegans. The Ins/Igf-1 signalling pathway in C.elegans consists of proteins encoded by *daf-2, age-1 (daf-26), akt-1, akt-2, daf12, daf-16* and *daf-18* genes. These genes are part of the *»dauer formation«* (daf) group of genes which regulate reproduction and the shift from a normal metabolic state to a metabolically inactive state, known as the »dauer larva« formation.

The first longevity mutant to be identified was the *Age-1* gene, which encondes a homologue of mammalian PI3K[36]. Age-1 mutants have a slower metabolic rate, display age-dependent elevations of copper/zinc superoxide dismutase (CuZn-SOD) and catalase, are resistant to oxidative stress and live 65% longer.

The main gene of the Ins/Igf-1 cascade is the *daf-2* gene which encodes an insulin-like receptor protein (DAF2) homologous to the separate insulin and Igf-1 receptors in vertebrates. Mutations which decrease the level of *daf-2* gene expression extend lifespan[37].

Genes encoding insulin-like proteins which bind to DAF2 and modulate metabolic response, are found in chemosensory neurons and are released in response to food sensing[38]. Worms with defects in chemosensory neurons show increase in lifespan up to 121%.

The inhibition of Ins/Igf-1 signalling pathway, i.e. the reduced insulin signalling, as well as CR, in C.elegans reduces fertility and increases lifespan possibly to delay reproduction until the period of limited food ends. These mutants have a slower metabolism, increased resistance to oxidative stress and express high levels of catalase and SOD, which shows that CR and the production of free radicals are related.

D. melanogaster. Genes involved in the Ins/Igf-1 signalling pathway in D.melanogaster show high homology with those in C.elegans. Decreased expression of the *Inr (insulin receptor)* gene which encodes the Ins/Igf-1 receptor (homologue of C.elegans DAF2r and human insulin and Igf-1 receptor) and the *chico* gene (Inr substrate) increase lifespan in females by 85% and 52%, respectively[39,40]. Both chico and Inr mutant adults are sterile which proves that Ins/Igf-1 regulates fertility and lifespan in response to nutrition. These long-lived mutants have reduced insulin signalling, increased levels of SOD and tryglycerids and reduced body size[40].

M. musculus. In mammals, the Ins/Igf-1 signalling pathway is more complex and contains separate receptors for insulin and Igf-1. Mutations of *Prop-1* (prophet-of-Pit-1) and *Pit-1* (pituitary-specific transcription factor 1) genes, which encode transcription factors involved in pituitary development, are known to extend lifespan. *Ames and Snell* dwarf mice are knockouts for *Prop-1* and *Pit-1* genes, respectively, and both have pituitary agenesis resulting in panhypopituitarism, short stature and infertility[41]. The lifespan of Ames mice is extended by 50% in females and 64% in males, while the lifespan of Snell mice is extended by 40% in both sexes[42]. The extended lifespan is thought to be the consequence of growth hormone (GH) and subsequently, Igf-1 deficiency. In the lack of GH and Igf-1 insulin release is reduces, tissue sensitivity to insulin increased and plasma glucose levels lowered[41]. A similar phenotype is observed for GH receptor knockout mice[43].

Dwarf mice with high levels of GH along with 90% lower levels of Igf-1 live longer than wild-type mice which indicates that low levels of Igf-1 but not GH are responsible for an extended lifespan[43]. Additional evidence that Igf-1 is responsible for increased lifespan comes from heterozygous Igf-1r knockout mice which show insensitivity to Igf-1 and 26% longer lifespan[44]. Thus, lifespan can be extended by either low levels of circulating Igf-1 or a general decrease in Igf-1 receptor levels.

Disruption of specific insulin receptor in adipose tissue extends longevity by 134 days (18%) in FIRKO (fat-specific insulin receptor knock-out) mice[45]. These mice have normal calorie intake but are protected from age-related obesity because the lack of insulin receptor in adipose tissue leads to absence of insulin signalling, reduces the transport of glucosis and aminoacids and impairs their conversion to fat which leads to decreased body mass. Adypocytes of FIRKO mice produce increased levels of leptins, which stimulate the hypothalamus to the production of metabolites which decrease calorie intake, increase energy expediture and decrease insulin production[46]. Mutations in the leptin gene, *Lep***,** causes downregulation of TOR (target of rapamycin) signalling, hyperphagia and massive obesity, along with decreased lifespan.

Klotho gene, which was identified in mouse models, encodes the klotho transmembrane protein homologous to mammalian lactase glycosylceramidase. *Klotho* is involved in glucosis metabolism through negative regulation of insulin and Igf-1 receptors and also regulates calcium metabolism[47]. Overexpression of *klotho* gene inhibits Ins/Igf-1 signalling pathway in mice, increases resistance to oxidative stress through the induction of SOD and extends lifespan. Disruption of *klotho* gene leads to decreased lifespan and premature onset of age-related diseases such as osteopenia and atherosclerosis[48]. The homology of klotho with mammalian lactase glycosylceramidase suggests that klotho might regulate sphingolipid metabolism whose products regulate cell cycle, replicative senescence and apoptosis. Recent studies have shown that homozygous KL-VS allele carriers have lower levels of high-density lipoprotein (HDL), higher systolic blood pressure, increased risk of stroke and shorter longevity[49].

Humans. In humans, patients with defect in the GH/Igf-1 axis have various health problems. Patients with Laron syndrome, an autosomal recessive disease caused by GH insentivity due to *GH receptor* gene mutation, have various medical problems but show increased lifespan and live up to 90 years of age[50].

Although the influence of Ins/Igf-1 signalling pathway on longevity in humans hasn't been well studied, there is

some evidence that it is involved in the aging process. Long-lived people and centenerians have increased tissue sensitivity to insulin, lower levels of circulating Igf-1 and preserved insulin action[51]. Decreased Igf-1 plasma levels probably reduce cellular proliferation and decrease the risk of cancerogenesis. It has been shown that centenarians have *Igf-1r* gene polymorphisms which are associated with lower plasma levels of Igf-1[52].

Cholesterol metabolism in humans. The most common age-related conditions have important nutritional components, such as cardiovascular diseases, diabetes, stroke, osteoporosis, cataract, and cognitive decline[53]. Susceptibility genes for human diseases also influence the aging process and genes involved in the pathogenesis of cardiovascular diseases seem to be a crucial determinant of human lonevity. The metabolism of lipoproteins and cholesterol influences longevity, and individuals with exceptional longevity have significantly larger HDL and LDL particle sizes[54]. This is associated with lower incidence of hypertension and cardiovascular diseases. Also, certain genotypes of *apolipoprotein E (apoE)*, influence lifespan through association with disease[55].

The *α and β liver-X-receptors (LRX)* are most similar to C.elegans daf-12 nuclear hormone receptor which regulates fertility and metabolism. In humans, the LRX regulate cholesterol metabolism. Certain polymorphisms are associated with increased lifespan and show protective effect from cardiovascular diseases[56].

In general, many benefits of CR are accompanied by a number of negative effects, especially delayed growth and changes in fertility, which makes it unsuitable for research in humans. It is well known that eating disorders, as in case of increased calorie intake, lead to obesity and premature onset of multiple disorders such as atherosclerosis, diabetes and cardiovascular diseases, while malnutrition as in case of anorexia nervosa leads to anovulation and secondary sterility[53].

Forkhead transcription factors (FOXO)

FOXO proteins are a subgroup of the Forkhead family of transcription factors and regulate tumor suppression, energy metabolism, and longevity. FOXO factors are key downstream targets of insulin, growth factors, nutrient, and oxidative stress stimuli and control numerous cellular functions[57]. In invertebrates, there is only one *FOXO* gene (*daf-16* in C.elegans, *dFOXO* in D.melanogaster) and four *FOXO* genes in mammals (*FOXO1a, 3a, 4, 6*). FOXO-dependent cellular responses include gluconeogenesis, neuropeptide secretion, atrophy, autophagy, apoptosis, cell cycle arrest, and stress resistance[57].

C. elegans. In response to insulin-like proteins, Daf-2 activates age-1 protein and leads to phosphorylation of a cascade of enzymes which ultimately regulate the nuclear translocation of daf-16[58]. The long-lived mutants have an active daf-16 protein. As the Ins/Igf-1 signalling pathway negatively regulates the activity of DAF-16, in the absence of insulin-like proteins, daf-16 is located in the nucleus where it induces expression of target genes involved in the induction of heat and stress resistance, fat storage, development arrest, fertility and metabolism[59].

Humans. Mammalian FOXO proteins, the target factors of Ins/Igf-1 signalling pathway, are phosphorylated and inhibited in response to insulin and growth factor stimulation[60]. FOXO target genes regulate glucose metabolism, cellular differentiation and energy consumption. Certain gene polymorphisms in *FOXO1a* and *FOXO3a* genes have been associated with higher glucose levels, increased risk of diabetes, the incidence of age-related diseases and shorter lifespan[61]. FOXO3a enhances the expression of the MnSOD and catalase antioxidant enzymes and is also an important sensor for cellular stresses, such as cytotoxic stress.

AMP-activated protein kinase. Recently, a lot of attention is paid to the *AMP-activated protein kinase* as a lifespan gene. AMPK is activated by a decrease in energy levels when it inactivates energy consumption pathways and activates energy production pathways. For instance, metabolic stresses which increase the cellular AMP:ATP ratio (such as hypoglycemia) activate the AMP Kinase (AMPK) system. AMPK protects cells against stresses by activating alternative metabolic pathways and inhibiting cell growth and division. AMPK directly regulates FOXO3, which then promotes resistance to oxidative stress and longevity and control energy balance and stress resistance in cells throughout life[62].

TOR signalling pathway

The target of rapamycin (TOR) proteins are an evolutionary conserved part of a protein family termed the phosphatidylinositol kinase-related kinases (or PIKKs), a large group of signaling molecules which function as Serine/Threonine protein kinases. The TOR regulates cell growth and metabolism in response to environmental stimuli. It integrates signals which coordinate cell growth, cell proliferation, cell motility, survival and cell cycle progression with sufficiency of nutrients, energy, and growth factors[63]. TOR signaling pathway is also a sensor of cellular redox status and regulates mitochondrial homeostasis and gene expression.

Various forms of stress and nutrient deprivation reduce TOR signaling which then stimulates CR, energy saving and leads to increased longevity. There is also a functional link between TOR and Ins/Igf-1 signalling pathway in worms, flies and mammals.

S. cerevisiae. Deletion of the *Tor1* gene extends chronological life span primarily by increasing mitochondrial respiration via enhanced translation of mtDNA-encoded oxidative phosphorylation complex subunits[64]. Tor1 also interacts with Sch9 (AKT homologue) and PKA (protein-kinase A) proteins and regulates cellular response to altered glucose and nitrogen levels[65]. Inhibition of Tor1, Sch9 and PKA activity increases lifespan, reduces stress response and transcription of ribosomal proteins by rDNA (ribosomal DNA) silencing.

C. elegans. Disruption of TOR and its regulatory protein Raptor causes developmental arrest, intestinal atro-

phy and increased lifespan[66]. The Raptor protein is encoded by *Daf-15* gene which is regulated by Daf-16. Although this increase in lifespan is independent of Daf-16, these results indicate that there is a cross-talk between TOR and Ins/Igf-1 signalling pathways which converge on Daf-15 to regulate larval development, metabolism and life span. Both of these pathways integrate nutrient sensing, calorie intake and influence longevity.

Mammals. Mammalian TOR (mTOR) is one of the most intruguing pathways associated with aging. This pathway regulates embryonic growth and development in response to nutrients and is also involved in the pathogenesis of numerous disease, indicating that aging and embryonic development share similar executive mechanisms. The mTOR integrates the signals from multiple upstream pathways, including insulin, insulin-like growth factors (Igf-1 and Igf-2), and mitogens.

Mice with disruption of mTOR die shortly after implantation due to impaired cell proliferation in embryonic and extraembryonic tissues[67]. The dysregulation of the mTOR pathway is implicated as a contributing factor to cancer, diabetes, obesity, cardiovascular diseases and neurological disorders[68]. Although the exact role of mTOR on longevity remains to be discovered, the fact that mTOR is associated with the onset of many age-related diseases indicated that research on this pathway may bring many key answers to aging process in mammals.

3. Genomic stability

Considering that DNA is continuously damaged by endogenous and exogenous agents and by intrinsic instability of chemical bonds within DNA, genomic instability is a crucial component of aging in all organisms. Genomic instability affects gene expression and protein production which can lead to cell death, cancer, various diseases, and overall functional decline[68]. Proposed mechanisms which affect the process of aging through genomic instability include DNA mutations, damage to cellular components, inefficient DNA repair and epigenetic mechanisms.

DNA damage

Point mutations, chromosome aberrations, mitotic recombination and other forms of DNA damage increase with aging in both invertebrates and vertebrates which makes cumulative damage to the nuclear and mitochondrial DNA one of the main causes of aging. Extensive DNA damage which cannot be repaired or which canges DNA metabolism leads to cellular sensescence or death. Numerous factors cause DNA damage, include exogenous (radiation, stress, and toxins) and endogenous factors (ROS, replication errors and chemical changes to the DNA). During aging all cells accumulate mutations, including the germline and it is well known that increasing parental age is the single most important risk factor for aneuploidic conceptions and miscarriage[69].

Although the somatic mutation theory supposes random damage, genes like *HLA,* repetitive and telomere sequences accumulate damage 2–3x faster than other genes[70]. Accumulation of DNA damage can result in loss of cellular and tissue functions through a combination of energy insufficiency, signalling defects, apoptosis, replicative senescence and aberrant gene expression which can in turn lead to many diseases and cancers.

As ROS are a source of chronic, peristant DNA damage, aging cells and organisms accumulate increased levels of oxidant-damaged nuclear and mitochondrial DNA (mtDNA). Oxidative damage to mtDNA is up to 20x higher than to nuclear DNA, due to its proximity to the source of oxidant generation, the fact that it lacks protective histone proteins and has a limited DNA repair system. In humans, mtDNA accumulates mutations progressively and there is also age-related decrease in the respiratory chain capacity in various tissues. Post-mitotic cells, are especially sensitive to the loss of mtDNA integrity which leads to mitochondrial functional decline and oxidative stress and might also contribute to development of Alzheimer's disease[71]. Certain mtDNA haplotypes are more common in centenerians and the degree of age-induced mutation in mtDNA varies among individuals indicating that the rate of aging might be influenced by the genetic structure of mtDNA.

DNA repair system

DNA repair system is needed for maintaining the intact structure and function of DNA as well as for ensuring genomic stability. During aging, the ability of DNA repair system decreases along with the accumulation of DNA damage[68].

p53. The *p53* tumor-suppressor gene is one of the most important genes implicated in the maintenance of genomic stability and has a crucial role in cellular responses to DNA damage. It is also called »cancer gene« due to its inactivation in over 80% of cancer[72]. In response to stress signals, *p53* becomes functionally active and induces either a transient cell cycle arrest, apoptosis or cellular senescence.

Studies on mouse models indicate association between the tumor suppressive and age-promoting functions of *p53*[72]. Overexpression of *p53* gene in mice decreases cancer incidence but these mice live shorter and show signs of premature aging. Several recent studies have shown that the common Arg72Pro polymorphism of *p53* gene is associated with increased longevity and cancer survival in humans[73].

WRN Helicase. There are several human premature aging syndromes which include defects in the nuclear DNA repair system, such as Xeroderma pigmentosum (XP), Werner, Bloom and Cockayne syndrome. *WRN* and *BLM* genes encode RecQ-like helicases involved in the nucleotide excision repair (NER) and telomere maintenance. Werner syndrome cells exhibit premature replicative senescence, defects in recombination, increased DNA damage and reduced DNA repair which leads to genomic instability and premature aging phenotypes[74]. WRN protein is also an exonuclease and plays significant roles in DNA replication and telomere maintenance.

Nuclear lamina

An important factor involved in maintaining the genomic stability in human cells is the structure of nuclear lamina and nuclear morphology. Nuclear Lamin proteins which build up the nuclear lamina regulate several nuclear processes such as transcription, chromatin organization and DNA replication, and maintain nuclear and cellular integrity[75]. Mutations in the *LMNA* gene, encoding A-type lamins, lead to cardiac and skeletal muscle disease, lipodystrophy and several premature ageing syndromes. LMNA defective cells show nuclear deformation, relocalization of heterochromatin and an upregulated DNA damage response.

Ribosomal DNA

Loss of genomic ribosomal DNA (rDNA) has been associated with cellular and organismal ageing. The rDNA genetic locus occupies a large part of the genome and thus, the condition of the rDNA, such as its stability, might affect cellular functions[76].

Aging in S.cerevisiae is determined by the replicative lifespan, i.e. the number of times an individual cell divides[77]. Studies on aging in S.cerevisiae have shown that aging is a result of progressive disregulation of the rDNA locus. The rDNA locus contains 100–200 tandem repeats of genes encoding rRNA which organize the nucleolus. During aging the production of rRNA increases, leads to the assembly of defective ribosomes and inefficient protein synthesis[77].

Homologous recombination of rDNA leads to formation of extrachromosomal rDNA circles (ERCs) which accumulate during each cell division up to a 1000 copies per mother cell[78]. Accumulation of these ERCs causes genomic instability and is one of the major causes of aging in yeast.

There has been some association between rDNA and aging in humans. It has been recently shown that during ageing a preferential loss of 5S and 28S rDNA genes can be seen in human adipose tissue[79].

Epigenetic Mechanisms and Aging

Epigenetics is the study of heritable and reversible changes in gene expression that occur without a change in DNA sequence. Epigenetic mechanisms, such as DNA methylation, histone modifications, chromatin remodeling, asynchronus DNA replication, and regulatory non-coding RNAs enable precise regulation of gene expression dependent on cell type and developmental period. Epigenetic modifications represent the link through which the environment interacts with the genome and modulates gene expression in response to external factors, such as diet and various stresses. Each differentiated cell type has its own epigenetic signature, which reflects genotype, developmental history, and environmental influences and ultimately reflects the phenotype of the cell and organism[80].

Histone modifications, as well as DNA methylation and probably other epigenetic modifications respond to metabolic state of the cell and other environmental stimuli, including stress.

Studies of twins and longlived families have estimated that 20–30% of the variation in human lifespan is determined by genetic factors, which impact becomes more important for survival at older ages. Monozygous twins exhibit remarkable differences in the overall content of DNA methylation and histone acetylation which affects their gene expression and leads to different phenotypes[81]. These data provide evidence that epigenetic variations during aging can also occur independently of the genetic sequence. This phenomenon is known as »epigenetic drift« and is attributed to the effect of different environments on the same genomic sequences.

During early embryonic development the genome of eutherian mammals undergoes dramatic changes in epigenetic mdifications in order to ensure proper differentiation[82]. After the completion of organogenesis, these modifications are stably maintained during each cell division. However, the genome is not a static structure, but rather goes through a lifelong remodelling that specifies and modulates expression of various genes which determine organism functions in relation to life period. During postnatal life, epigenetic modifications are not fixed, but are constantly changing, either in response to environmental stimuli either spontaneously. Thus, aging is part of the normal ontogenesis which follows embryonic and postnatal development and is indeed genetically determined, i.e. the consequence of extensive continuous genetic/epigenetic changes.

Considering that the epigenetics of aging involves complex and extensive mechanisms, here we will give only a brief overview on the impact of DNA methylation and histone modifications on the aging process.

1. DNA methylation

DNA methylation, the addition of a methyl group to 5 position of cytosine pyrimidine ring, in adult somatic tissues, typically occurs in a CpG dinucleotide context (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide and are separated by a phosphate which links the two nucleosides together in the DNA). During aging somatic cells undergo alterations in the amount and pattern of DNA methylation on the global and tissue-specific level.

Global DNA methylation decreases during aging in various cell types[83]. Although the exact cause and mechanism by which this global hypomethylation occurs remains unknown, one of the reasons might be the progressive decline in DNA methyltransferase 1 (Dnmt1) activity which leads to passive demethylation. Global hypomethylation of genomic DNA is a common characteristic of aging and cancerogenesis, which indicates that accumulation of epigenetic alterations might be an important factor for neoplastic transformation[84].

Age-related methylation changes also occur in a tissue-specific manner and include gene promoters, as well as noncoding DNA sequences. Gene promoters rich with CpG islands become hypermethylated during aging, most likely as a consequence of increased Dnmt3b de novo methylation activity[85]. Hypermethylation of estrogen receptor promoter in cardiovascular system with increasing age may play a role in atherogenesis and aging of the cardiovascular system[86].

Another example of promoter hypermethylation involves the *Insulin-like growth factor 2* gene (Igf-2) which is a genomically imprinted gene expressed only from paternal allele and encodes the major fetal growth factor. During aging, the Igf2 promoter methylation becomes more extensive and spreads on the paternal allele, resulting in biallelic promoter methylation which can lead to aberrant Igf-2 expression[87]. High levels of Igf-2 increase the risk of cancer and accelerate development of atherosclerosis and numerous age-related diseases. As previous studies indicate, genetic variations which regulate epigenetic mechanisms during development are also important determinants of aging process. We have shown that SNPs in Igf-2 gene are crucial for embryonic development and successful pregnancy outcome[88]. Several Igf-2 genotypes are associated with the rate of aging through population studies. As Igf-2 has a crucial role in embryonic development and as it shows dramatic DNA methylation changes during aging, it could be one of the most important determinants of the aging process, especially because of its role in the pathogenesis of age-related diseases. Thus, future studies are needed to further evaluate the role of Igf2 in aging.

The loss of epigenetic control, in sense of global hypomethylation as well as promoter hypermethylation, alters gene expression and leads to genomic instability which in turn promotes cell senescence, death or cancerogenesis. Age-dependent methylation and histone modifications changes are also involved in the development of several age-related diseases such as neurologic disorders, autoimmunity and cancer[89]. These progressive changes in DNA methylation were proposed to be a cellular counting mechanism which triggers senescence[90]. Along with embryonic downregulation of telomerase, alterations in DNA methylation pattern during aging could be a genetically determined »post-embryonic counting« mechanism, a »time-bomb« which is set after fertilization and dictates lifespan thereafter.

Fetal programming. Interindividual variations in DNA methylation patterns occur due to alterations in diet, genetic polymorphisms, lifestyle exposures and various environmental factors. Diet has been shown to dynamically affect DNA methylation status. For example, folate is involved in the synthesis of SAM (S-adenosyl-methionine), the universal methyl donor, and thus, changes in folate sources can lead to aberrant DNA methylation. DNA methylation is essential for early embryonic development and folate deficient diet, as well as certain polymorphisms in genes involved in folate metabolism, have been implicated in neural tube defects, Down's syndrome and numerous pregnancy complications, including recurrent spontaneous abortion[91].

Considering the critical roles that epigenetic modifications play in mammalian growth and development, early nutritional influences on these components could have an important role in human health[92]. Prenatal and early postnatal nutritional influences on epigenetic gene regulation represent a link between early nutrition and later metabolism and susceptibility to age-related diseases including cardiovascular diseases, type 2 diabetes, obesity, and cancer[93,94]. This phenomenon is called »fetal programming« and again points to the fact that there is a link between nutrition, embryonic development and aging and that these are not separate processes but rather different stages of the same developmental process.

2. Histone modifications

Modifications to N-terminal tails of histone proteins (acetylation, deacetlyation, ubiquitination etc), which can lead to chromatin remodelling, are sufficient to regulate gene expression levels and epigenetically alter gene functioning. Epigenetic regulation through histone modifications might be an important regulator of the cellular senescence phenotype.

Since the discovery of Sirtuins and epigenetic regulation of telomeres, it has become clear that chromatin remodeling plays an important role in aging and cellular senescence.

Telomeres and cellular senescence

Cellular senescence is the process which limits the number of cell divisions and results in irreversible cell cycle arrest with characteristic morphologic and functional alterations of the cell[95]. This replicative limit is also known as »Hayflick phenomenon or limit«. There are two kinds of cellular senescence, replicative and stress-induced premature senescence (SIPS).

Replicative senescence results from the progressive shortnening of telomeres, the specialized chromatin structures composed of repetitive DNA sequences (TTAGGG) and binding proteins which are located at the ends of chromosomes and serve to protect these areas from recombination, fusion and degradation. During each cell division telomeres continuously lose TTAGGG repeats because DNA polymerase cannot extend the linear ends of DNA molecule. This progressive telomere shortnening represents a form of »genetically determined molecular clock« which determines cellular senescence and death[96]. Telomerase, the enzyme which maintains telomere lenght by adding telomeric repeats, is expressed only in the most proliferative cells such as trophoblast cells, germ line cells, embryonic stem cells, lymphocytes, skin and intestine epithelium and hair follicle cells.

It is likely that replicative senescence is a form of prevention from genomic instability and cancerogenesis in aged cells. The GGG triplets represent sites of frequent oxidative damage which provides protection against damage to other areas in the genome, but at the same time

this also increases the rate of telomere shortening and aging[97]. Post-mitotic cells with high metabolic rates and increased oxidative stress, such as cardiomyocytes, express telomerase which protects telomeres and promotes survival[98]. Approximately 90% of all tumors upregulate telomerase which helps the cells to overcome a limited proliferative capacity and become immortalized due to the bypass of cellular arrest.

Mouse models have been crucial for the understanding of the basic molecular mechanisms of telomere function in aging and age-related diseases. Late-generation of mice deficient for *Terc* gene, which encodes a telomerase RNA component, show progressive telomere shortening, have shortened lifespan and develop numerous age-related diseases, including heart failure, immunosenescence, tissue atrophies and sterility[99].

Similar to this, in humans, short telomeres are associated with many age-related diseases, such as coronary atherosclerosis, vascular demention and Alzheimer's disease[100]. Humans with shorter telomeres have worse survival and increased mortality from heart and infectious disease.

It seems that short telomeres represent a form of DNA damage which influences the loss of cell viability. In mice which lack telomerase, short telomeres upregulate *p53* tumor-suppressor gene, a crucial mediator of cellular response to DNA damage, which induces apoptosis and protects from further damage and cancerogenesis[101]. Telomerase and p53-deficient mice have suppressed aging phenotype but develop an increased number of carcinomas which indicates that short telomeres contribute to genomic instability[102].

Several human premature aging syndromes are characterized by a faster rate of telomere shortening due to mutations in genes involved in the regulation of telomere state[103]. One of these syndromes includes dyskeratosis congenita (DC) which is caused by mutations in genes encoding for components of the telomerase complex. Mutations affect either the *Terc* or *Tert* gene encoding the RNA and enzymatic components of telomerase, respectively, or *DKCN1* gene which encodes dyskerin, a protein involved in rRNA processing, ribosome biogenesis and Terc stability. Patients with DC have increased risk of cancerogenesis and develop multiple pathologies similar to those seen in telomerase-deficient mice which are the consequence of defects in telomerase activity, telomere shortening and genomic instability[104].

Stress-induced premature senescence (SIPS). SIPS occurs in response to numerous environmental stressors (ionizing radiation, free radicals, ethanol, DNA damage etc) and prematurely induces the same phenotypes as replicative senescence prior to Hayflick limit[105]. These adverse factors lead to telomere shortening, negatively impact telomerase activity and activate *p53* gene which induces apoptosis. SIPS protects from genomic instability induced by DNA damage and is most likely the molecular response to cumulative damage during aging.

Other epigenetic factors regulating telomere shortening. It seems that not only the telomere lenght but also overall telomere structure is important in cellular senescence. The NAD^+-dependent histone H3K9 deacetylase encoded by *SIRT6* gene, modulates telomeric chromatin structure through histone deacetylation and its depletion leads to abnormal telomere structure and dysfunction, end-to-end chromosomal fusions and premature cellular senescence[106].

Certain tissues with little mitotic activity, such as liver, show progressive telomere shortening during aging, indicating that there must be factors other than cell division which modulate the attrition of telomeres[107]. Also, several external factors, such as hydrogen peroxide and gamma radiation, cause premature senescence by inducing damage throughout the genome and affect telomere structure without telomere shortening[107].

Sirtuins

Sirtuins (Sir, Silent Information Regulators) or class III histone deacetylases are a gene family of NAD-dependent protein deacetylases and ADP-ribosyltransferases, which are evolutionary conserved and activated during response to stress in order to protect and stabilize the genome. As Sirtuins are regulated by the nicotinamide adenine dinucleotide (NAD) cofactor and serve as sensors of the metabolic state of the cell.

S. cerevisiae. The major genetic determinant of replicative lifespan in yeast is the *Sir2* gene[108]. An important manifestation of the aging process in yeast is the loss of genomic silencing at the telomeric regions and silent mating-type loci (HML and HMR) which leads to genomic instability and sterility. Silencing of the yeast genome is carried out Sir 2,3 and 4 which form a complex that mediates genomic silencing at HML/HMR and telomere regions. Mutation which leads to overexpression of *Sir4* gene redirects the Sir 2/3/4p complex from HML/HMR and telomeres to the nucleolus, the localization of rDNA genes and a major site of ribosome biogenesis, which extends lifespan by 30%[108].

Overexpression of *Sir2* gene increases lifespan by 50% because the Sir2 protein (Sir2p) silences chromatin, enables DNA repair, maintaines chromosome fidelity during meiosis, mediates silencing at the rDNA region, inhibits rDNA recombination and also represses transcription of inserted genes[108].

Calorie restriction also activates *Sir2* gene expression which then leads to reduction in rDNA recombination[109]. Polyphenol resveratrol activates sirutins and also has antioxidant and anti-inflammatory properties. Resveratrol increases replicative lifespan in yeast which indicates that sirtuins regulate metabolism through calorie intake and free radical production[110].

Mammals. In mammals, there are seven sirtuins, *SIRT1-7*, which deacetylate both histone and non-histone proteins. They are involved in the regulation of gene expression, DNA repair, apoptosis, cell cycle and insulin regulation. Mammalian sirtuins promote longevity by

limiting replicative lifespan and thus, protecting against oxidative stress and cummulative DNA damage. The loss of sirtuin expression or function bypasses replicative senescence, allows cell to divide without the proper repair of DNA which allows accumulation of mutations and increases the risk of cancerogenesis[111].

SIRT1 is known as the guardian against cellular oxidative stress, DNA damage but is also involved in the regulation of metabolism. The SIRT1 protein promotes cellular survival under stress conditions by inducing cell-cycle arrest and DNA repair through deacetylation of p53, FOXOs, Ku70 and Nf?B[112]. In cultured human hepatocytes SIRT1 deacetylates FOXO1 which promotes transcription of gluconeogenic genes upon stress, represses apoptosis and induces resistance to stress[113].

Polyphenols, including resveratrol, increase SIRT1 deacetylase activity, LKB1/STK11 (serine/threonine kinase 11) phosphorylation and as it has been recently shown, the SIRT1 functions as a novel upstream regulator for LKB1/AMPK signaling[114].

SIRT6 is a nuclear protein with ADP-ribosyltransferase activity and is involved in the base excision repair system (BER). SIRT6 knockout mice have a deficiency in the BER system and show increased sensitivity to DNA damage, chromosome aberrations and centromere dysfunction which results in global genomic instability[115]. These mice die within a month after birth and show premature aging symptomes, including the loss of subcutaneous fat and decreased bone density.

Discussion – The Phenomenon of Aging and Reproductive Genetics

Most of the studies on animal models have shown that aging is inevitably related to reproduction. Genetic manipulations which extend lifespan through alterations in metabolic pathways and stress repsonse, also reduce fertility possibly to postpone reproduction until the period of limited nutrient sources ends.

Aging is an irreversible process which involves deterioration of physiological functions, loss of viability, development of chronic diseases and cancer which result in death. Aging is also inevitably related to decline in reproductive function. Reproduction is the main determinant of the life cycle of every species. It is estimated that up to 70% of fertilized ova are lost, making the process of human reproduction quite unsuccessful. The incidence of unsuccessful pregnancy rises with parental, especially mother's age, regardless of fetal viability. In older women, oocytes show increased number of chromosomal abnormalities and the endometrium becomes less receptive[116]. The majority of trisomy 21 (Down syndrome) are caused by chromosome nondisjunction and at least 90% of cases are due to maternal errors which occur during oogenesis[117]. During aging, environmental and age-related damage accumulate in the arrested oocytes making the increased mother's age the most significant risk factor for chromosomal nondisjunction.

As fertility in women is directly associated with chronological age, menopause could be defined as a genetically and hormonally regulated mechanism of protection against aneuploidic concepts and against rising age-specific maternal mortality risks[118]. This is a possible mechanism by which evolution protects the human genome against »genetic burden« which would compromise the survival of the species. It is most likely that reproduction is only a mechanism which allows the quality modification, trasnmission and improvement of genetic material, and that evolution shapes the genomes for reproductive success and not for post-reproductive survival which ensures the preservation and progress of species. This is supported by the fact that the process of aging highly progresses in the post-reproductive period which coincides with the onset of most chronic diseases, cancers and dementias which compromises survival[119]. Aging would thus be a protective mechanism which ensures resources for new genetic combinations and their adaptation and survival in diverse conditions.

Discussion and Conclusion

Aging and longevity are genetically regulated, but not pre-programmed processes due to the fact that environmental factors influence the rate of aging. The fact that individuals within a species have equal lifespans supports the theory that aging is a genetically influenced process and regardless of the fact that lifespan is continuously increasing, there is a limit of human longevity which is approximately 120 years. Thus, an organism's maximum lifespan potential is genetically determined but individual variation in lifespan among individuals of the same species indicates that the process of aging is a consequence of an inseparable link between the genome and environment due to the fact that external factors constantly interact with the genome. Perhaps the most obvious evidence comes from studies of monozygotic twins where we would expect the same or similar process of aging due to the fact that they share the same genetic sequences. However, even here the singular and unique environmental factors shape the genomes in different directions, which is known as »epigenetic drift«. Studies of twins and long-lived families suggest that approximately 20–30% of the variation in human lifespan is determined by genetic factors, which becomes more important for survival at old age[120].

From an evolutionary perspective, aging limits the reproductive potential and as such should be opposed by natural selection and thus, most gerontologists believe that there are no genes which cause aging. The fact that »longevity genes« or »gerontogenes« have not yet been found could be explained by the fact that aging is probably a physiological process which normally follows embryonic and postnatal development and genes regulating these processes also probably control aging.

Series of studies have demonstrated that age-related diseases take root in early nutrition, during gestation and lactation which is known as »fetal programming«. It

is well known that low birthweight and short body length at birth are associated with increased risk of developing cardiovascular disease, obesity and type 2 diabetes in adult life. The fetal programming hypothesis proposes that these diseases originate through adaptation which the fetus makes when it is undernourished and the functions which are set prenatally determine the function and the structure of the body in adult life. The link between fetal growth and age-related diseases involve extensive changes in gene expression, which makes the epigenetic modifications one of the most important regulators of the aging process.

As shown in this review, most of what we know on the process of aging in humans comes from animal models, human cells and human premature aging syndromes. The existence of genes which influence lifespan in various species points to the fact that aging is an evolutionary conserved process. All of the genes so far identified as longevity genes are involved in stress resistance, metabolic pathways and maintenance of genomic integrity. In humans, the susceptibility genes for certain diseases also influence the aging process. The importance of genes involved in cardiovascular diseases seem to be a crucial determinant of human longevity since they represent the primary cause of death in the modern world. For example, certain apolipoprotein E genotypes influence lifespan through association with disease. Other proposed candidate genes might involve metabolic genes, immune-system genes, mtDNA mutations, DNA repair system genes and genes regulating telomere length – the genes whose function clearly declines and changes later in life[121]. Single nucleotide polymorphisms (SNP) are the most common type of genetic variations and can determine changes in gene expression which can be a factor of susceptibility to various diseaseas and even aging. The research on SNPs in long-lived humans might lead to discovery of gene candidates associated with aging. As telomere lenght and epigenetic modifications are heritable, it could be possible that genetic variations between individuals, which affect telomere structure and epigenetic modifications, are important determinants of longevity and development of different age-related diseases.

The genome is an extremely dynamic structure. Throughout life, epigenetic modifications are not fixed, but are constantly changing in response to environmental stimuli which modulates gene expression. Environmental conditions in which the genome is set play an exceptional role in the modification and regulation of developmental processes. As it has been recently stated, the physiological hypoxia of the first trimester gestational sac may protect the developing fetus against the deleterious and teratogenic effects of reactive oxygen species[122]. On the other hand, excessive production of ROS during later stages of development gradually damages the cell and leads to loss of function and cell viability. This indicates that aging is a part of normal ontogenesis and is the consequence of the »communication« between the genome and environment and extensive and continuous genetic/epigenetic changes. Alterations in DNA methylation pattern and progressive telomere shortening during aging represent a genetically determined »post-embryonic counting« mechanism, a »time-bomb« which is set after fertilization and dictates lifespan thereafter. Thus, future studies on epigenetic mechanisms and their dynamic changes through lifetime might provide key answers to many questions related to aging.

Researches which regard aging only as a pathophysiological mechanism will not provide answers. As aging is a multidimensional process of genetic, physical, psychological, and social changes, the complete understanding of aging mechanisms will be possible only through an integrative approach.

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S. Ostojić

Department of Biology and Medical Genetics, School of Medicine University of Rijeka, Braće Branchetta 20, 51000 Rijeka, Croatia
e-mail address: sasa@medri.hr

GENETIČKI I EPIGENETIČKI POGLED NA PROCES STARENJA U ČOVJEKA

S A Ž E T A K

Proces starenja je jedan od najsloženijih i najintrigantnijih bioloških fenomena. Starenje je genetički reguliran proces u kojem je maksimalni životni vijek organizama predodređen, dok brzina starenja ovisi o okolišnim čimbenicima i životnom stilu. S obzirom na složenost mehanizama uključenih u regulaciju procesa starenja, do danas ne postoji jedinstvena, sveobuhvatna teorija koja ih može objasniti. Kako genetički/epigenetički, kao i okolišni čimbenici neizbježno utječu na proces starenja, ovdje donosimo pregled genetičke i epigenetičke regulacije najvažnijih molekularnih i staničnih mehanizama uključenih u proces starenja. Također dajemo pregled ključnih genetičkih i molekularnih puteva povezanih sa starenjem, temeljenih na istraživanju oksidativnog stresa, metabolizma, genomske stabilnosti, epigenetičkih modifikacija i staničnog starenja u životinjskim modelima i čovjeka. Kako većina genetičkih modifikacija koje utječu na proces starenja istovremeno utječu i na reprodukciju u čovjeka, raspravljamo o starenju kao postreproduktivnom genetički određenom procesu. Nakon reprodukcije starenje ubrzano napreduje što se klinički podudara sa nastupom većine kroničnih bolesti, tumora i demencija. Kako evolucija oblikuje genome za reproduktivni uspjeh a ne za postreproduktivno preživljenje, starenje se može definirati kao zaštitni mehanizam koji osigurava očuvanje i napredak vrste kroz kvalitetnu modifikaciju, prenošenje i poboljšanje genetičkog materijala.