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Mechanisms of vascular aging

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ABSTRACT

Vascular aging plays a key role in morbidity and mortality in the elderly. With age, the vasculature undergoes changes characterized by endothelial dysfunction, wall thickening, decreased elongation, and arterial stiffness. The review focuses on the main cellular and molecular mechanisms of aging, including oxidative stress, endothelial dysfunction, inflammation, increased arterial stiffness, and molecular genetic aspects. Their role in the pathogenesis of diseases associated with aging is considered. Some of the molecular mechanisms underlying these processes include increased expression and activation of matrix metalloproteinases, activation of transforming growth factor β1 signaling, increased levels of C-reactive protein, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)α, and N-terminal pro B-type natriuretic peptide (NT-pro-BNP), and activation of proinflammatory signaling pathways. These events can be caused by vasoactive agents, such as angiotensin II and endothelin-1, the levels of which increase with aging. For prevention of cardiovascular diseases, it is important to understand the mechanisms underlying age-related pathophysiological changes in the blood vessels.

Keywords: vascular aging, cardiovascular disease, oxidative stress, endothelial dysfunction

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Механизмы сосудистого старения

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РЕЗЮМЕ

Старение сосудистой системы играет ключевую роль в заболеваемости и смертности среди пожилых людей. С возрастом сосудистая сеть претерпевает изменения, характеризующиеся дисфункцией эндотелия, утолщением стенок, снижением растяжимости и артериальной жесткостью. В данном обзоре уделяется

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внимание основным клеточным и молекулярным механизмам старения, включая окислительный стресс, эндотелиальную дисфункцию, воспаление, повышенную артериальную жесткость; молекулярно-генетическим аспектам. Рассматривается их роль в патогенезе заболеваний, связанных со старением. Некоторые молекулярные механизмы, лежащие в основе этих процессов, включают повышенную экспрессию и активацию матричных металлопротеиназ, активацию передачи сигналов трансформирующего фактора роста β1, повышение концентрации С-реактивного протеина, интерлейкина-1, интерлейкина-6, фактора некроза опухоли α и натрийуретического пептида N-концевого про-В-типа, активацию провоспалительных сигнальных путей. Эти события могут быть вызваны вазоактивными агентами, такими как ангиотензин II, эндотелин-1, концентрация которых увеличивается при старении. Для профилактики сердечно-сосудистых заболеваний важно понимание механизмов, лежащих в основе возрастных патофизиологических изменений сосудов.

Ключевые слова: сосудистое старение, сердечно-сосудистые заболевания, окислительный стресс, эндотелиальная дисфункция

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INTRODUCTION

Cardiovascular diseases are the most common cause of death worldwide. At the same time, vascular aging is the main and irreversible risk factor for disease development [1–4]. Obviously, aging leads to certain changes that make cardiovascular system predisposed to diseases even in the absence of traditional risk factors, such as hypertension, diabetes mellitus, smoking, etc. [5]. Although aging is inevitable, gaining knowledge about the mechanisms underlying this process in the cardiovascular system has changed the perception of vascular aging as a modifiable risk factor [6]. At the molecular and cellular levels, aging is associated with structural, mechanical, and functional changes in blood vessels, characterized by increased arterial stiffness, decreased nitric oxide production, increased production of reactive oxygen species (oxidative stress), and endothelial dysfunction.

Cardiovascular aging reduces the contractile and mechanical efficiency of blood vessels. Specific changes include increased smooth muscle tone, increased collagenolytic and elastolytic activity, and arterial wall thickening. These changes contribute to an increase in systolic blood pressure, an increase in cardiac load, and systemic vascular resistance [7]. Progressive hypertrophy of cardiomyocytes, inflammation, and gradual development of cardiac fibrosis are signs of cardiac aging [8]. Age-related arterial wall remodeling contributes to the pathogenesis of vascular diseases leading to an increase in morbidity and mortality.

Thus, arterial aging is the main factor contributing to an increase in the incidence and prevalence of cardiovascular diseases, mainly due to chronic inflammation of arteries. Inflammatory signaling driven by the angiotensin II cascade causes unfavorable age-related structural and functional remodeling of arteries [9].

In order to prevent an increase in mortality from cardiovascular diseases in aging population, it is necessary to understand the mechanisms underlying age-related pathophysiological changes in blood vessels, including oxidative stress, mitochondrial dysfunction, and chronic inflammation.

ENDOTHELIAL DYSFUNCTION IN AGING

Vascular endothelium is a dynamic structure that performs many vital functions. The vascular endothelium must constantly maintain a balance between oxidants and antioxidants, vasodilators and vasoconstrictors, pro- and anti-inflammatory molecules, and

pro- and antithrombotic signals. Endothelial function in young people is regulated by traditional risk factors for cardiovascular diseases, but old age is independently associated with the development of vascular endothelial dysfunction [10]. Increased prevalence of cardiovascular diseases in aging is caused by aging of vascular endothelial cells and the associated vascular dysfunction. Aging of endothelial cells is a pathophysiological process involving functional and structural changes, such as dysregulation of vascular tone, increased endothelial permeability, arterial stiffness, impaired angiogenesis and vascular repair, and decreased mitochondrial biogenesis in endothelial cells [11].

Among various mechanisms leading to vascular dysfunction, endothelial dysfunction is one of the earliest and most important events. Impaired endothelial vasodilation is an early sign of vascular aging, preceding clinical manifestations of vascular dysfunction. It is also the first step toward cardiovascular diseases. [6]. Many pathophysiological changes in the endothelium contribute to vascular dysfunction associated with aging, such as decreased nitric oxide (NO) production and activation of calcium signaling (Ca^{2+}), increased endothelial permeability, impaired angiogenesis and vascular repair, and decreased mitochondrial biogenesis in endothelial cells. Thus, cell cycle regulation, oxidative stress, altered Ca^{2+} signaling, and vascular inflammation are involved in the pathophysiological process [11]. In addition, the accumulation of genetic damage changes normal expression and activity of genes, which leads to cellular senescence and vascular dysfunction [11]. Both macrovascular and microvascular endothelial dysfunction are the key markers of endothelial health and independent predictors of cardiovascular risk in the elderly [12].

OXIDATIVE STRESS IN AGING

Oxidative stress is involved in the pathology of many human diseases. Oxidative stress is recognized as a major factor in the pathophysiology and pathogenesis of such age-related diseases as metabolic syndrome, atherosclerosis, osteoporosis, obesity, dementia, diabetes, cancer, and arthritis [7, 13, 14]. Constant formation of free radicals, mainly reactive oxygen species (ROS), is the main characteristic of all living systems that use oxygen for their metabolism. The most common ROS are superoxide radical (O^{2-}) and hydrogen peroxide (H_2O_2), which can stimulate sequential reactions causing further free radical production and associated oxidative damage to cellular components. Oxidative stress and inflammation induce endothelial dysfunction resulting from decreased NO bioavailability [10]. Oxidative stress is involved in the pathogenesis of arterial stiffness, since oxidative damage can lead to increased vascular inflammation and cell proliferation, which can subsequently result in impaired arterial elasticity [15]. Oxidative stress in endothelial cells increases with age. It is caused by increased production of intracellular enzymes (NADPH oxidase and endothelial NO synthase (eNOS)), as well as by mitochondrial respiration in the absence of a corresponding increase in antioxidant defense regulated by appropriate transcription factors [10].

VASCULAR INFLAMMATION AND MARKERS OF INFLAMMATION IN AGING

Aging is associated with chronic low-grade inflammation (sterile inflammation), i.e. a type of inflammation caused by mechanical trauma, ischemia, and stress. Chronic inflammation is associated with many pathological conditions related to aging, for example, atherosclerosis, Alzheimer's disease, etc. [16]. Inflammation is characterized by increased expression of inflammatory cytokines, adhesion molecules, and endothelial cell chemokines. Aging is associated with increased levels of circulating cytokines and proinflammatory markers. Age-related changes in the immune system, known as immune aging, and increased secretion of cytokines by adipose tissue are the main causes of chronic inflammation [17]. Chronic inflammation is thought to be related to dysfunction of immune cells, such as cell migration and signaling of pattern recognition receptors (PRRs), which are necessary to respond to pathogens. This immune dysregulation can affect conditions associated with chronic inflammation (atherosclerosis and Alzheimer's disease). The mechanisms underlying this inflammation seem to include changes in the number and function of innate immune cells and PRR activation by endogenous ligands which leads to cytokine secretion [18].

In addition, a proinflammatory response is associated with activation of nuclear factor-kappa B (NF-κB) signaling, which is an important nuclear transcription factor that promotes expression of inflammatory cytokines in endothelial dysfunction and cardiovascular diseases [10]. Alarmins mediating sterile inflammation contribute to aging. At the same time, activation of metalloproteinase-2 (MMP-2) is worth noting. It is responsible for S100A9 alarmin degradation, which limits signals that cause inflammation [16].

An age-related increase in such inflammatory peptide biomarkers as interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) [19] is one the most studied markers of aging. Higher plasma concentrations of such inflammatory factors as IL-6 and TNF-α were associated with lower muscle mass and lower muscle strength (smaller muscle area, lower appendicular muscle mass with lower grip strength). It demonstrated a relationship between immune and functional status in the body of an elderly person [20]. CRP was associated with all causes and mortality, and IL-6 was found to be a predictor of mortality [21, 22]. However, when studying markers of inflammation, it turned out that centenarians have fewer signs of inflammation [23, 24]. Inflammatory peptides are either absent or lower in centenarians compared with younger cohorts, while the levels of anti-inflammatory cytokines, such as IL-10 and transforming growth factor (TGF)-β, are increased [25].

Adipokines, such as adiponectin, leptin, and visfatin, are regulators of inflammation [26]. It is interesting that adiponectin concentration changes with age and is associated with age-related health effects [27]. In the study including healthy elderly people aged 69–79 years, higher adiponectin levels were associated with an increased risk of overall and cardiovascular mortality [28].

Traditionally, N-terminal pro B-type natriuretic peptide (NT-pro-BNP) and troponin have been associated with myocardial injury and heart failure. NT-pro-BNP measurements provide predictive information about mortality and serious cardiovascular events in addition to traditional risk factors. NT-pro-BNP was a stronger biomarker of cardiovascular diseases and death risk than CRP in non-hospitalized individuals aged 50–89 years [29]. The study of 4,979 respondents (2,567 men and 2,412 women) who were divided into six age groups concluded that age over 70 years and male sex were associated with increased levels of NT-pro-BNP (> 400 pg / ml) (odds ratio (OR) 1.41; 95% confidence interval (CI) 1.20–1.65 for males) [30]. Despite their reliability as predictors of cardiac damage and cardiovascular diseases, both NT-pro-BNP and troponin increase with age, which successfully characterizes them as biomarkers of human aging [31].

INCREASED ARTERIAL STIFFNESS IN AGING

Increased arterial stiffness is an independent predictor of cardiovascular diseases that does not depend on blood pressure. Blood vessels undergo structural and functional changes characterized by remodeling (thickening) of the arteries, vascular fibrosis, and stiffness, which are manifested in aging and hypertension. Arterial stiffness is common and occurs in over 60% of people over 70 years of age and is a major independent predictor of serious cardiovascular events [32].

Arterial stiffness is assessed by pulse wave velocity measurement, pulse wave analysis, arterial stiffness analysis using 24-hour ambulatory blood pressure monitoring, and endothelial function assessment. Aortic stiffness causes an increase in pulse wave velocity and early reflection of waves with increased central hemodynamic load, which leads to damage to small arteries [33]. Patients with early vascular aging are at an increased risk of developing cardiovascular diseases. Its main component is arterial stiffness measured by an increased carotid-femoral pulse wave velocity [34].

Profibrotic processes play a significant role in the development of vascular stiffness. Fibrosis occurs in both large and small arteries. In large vessels, arterial stiffness leads to hemodynamic damage to peripheral tissues, which results in impaired endothelial function and increased vasomotor tone [32].

At the molecular and cellular levels, vascular aging and vascular changes are associated with increased expression and activation of matrix metalloproteinases (MMP), activation of transforming growth factor-b1 signaling, activation of galectin-3, and activation of proinflammatory and profibrotic signaling pathways. These events can be caused by such vasoactive agents as angiotensin II, endothelin-1 (ET-1), and aldosterone, the number of which increases with age [32].

THE ROLE OF MATRIX METALLOPROTEINASES IN VASCULAR REMODELING

In healthy vessels, deposition and exchange of extracellular matrix proteins are regulated, and the collagen / elastin ratio remains relatively constant. The imbalance of these processes leads to excessive deposition of extracellular matrix proteins, especially collagen and fibronectin, which contributes to vascular fibrosis and arterial stiffness in aging [32]. Extracellular matrix proteins are regulated with the help of metalloproteinases. In turn, they are activated by many factors associated with aging, such as interleukins, growth factors, and vasoactive agents.

Activated MMPs are capable of destroying collagen, elastin, and other extracellular matrix proteins, leading to aging and atherosclerotic effects in the arterial wall, for example, fibrosis, calcification, en-

dothelial dysfunction, and increased intima – media thickness, which further affects vascular remodeling and arterial stiffness [35–37]. Arterial remodeling mediated by MMP activation is a histopathological feature of aging arteries, hypertension, and atherosclerosis [35]. An imbalance between the activity of MMPs and their endogenous tissue inhibitors (TIMPs), which are produced by various cell types, including fibroblasts and macrophages, is important for extracellular matrix remodeling and arterial stiffness [15]. MMP-1 contributes to aging of endothelial cells through p53 activation [38].

In ischemic cardiomyopathy with progressing heart failure, there are mainly processes of collagen destruction in the extracellular matrix. They are accompanied by an increased MMP-1 level [39]. MMP-2 plays a major role in degradation of the extracellular matrix, supporting both angiogenesis and apoptosis of endothelial cells. An intermediate MMP-2 form supports survival and migration of the cells, while a fully active MMP-2 form leads to endothelial cell death. The p38 apoptotic pathway enhances synthesis and activation of the intermediate MMP-2 form. Caspases enhance synthesis and complete activation of MMP-2, but decrease the intermediate MMP-2 form [40]. In addition, MMP-2 promotes platelet aggregation and thrombus formation in response to arterial damage, and inactivation of the MMP-2 gene prevents thrombosis caused by weak stimuli in mice [41]. When studying age-related changes in MMP activity in animal models, a decrease in MMP-2 activity and an increase in MMP-9 activity with increasing age were found [42].

When studying the pathophysiology of aging in humans using the example of a healthy population of different ages, including centenarians (≥ 95 years), it was found that the MMP-2 serum activity is increased in centenarians compared with younger subjects. The authors suggested that the observed increase in MMP-2 in old age may play a positive role in achieving longevity [43].

MMP-9 is a major mediator of increased stiffness in the aging left ventricle. Aging is associated with increased MMP-9 expression in the left ventricle and decreased cardiac function. [44]. Elevated blood levels of MMP-9 and MCP-1 are positively correlated with an increase in end-diastolic volume, indicating that MCP-1 and MMP-9 are potential circulating biomarkers of cardiac aging. Increased density of macrophages in the left ventricle and stable co-localization of MMP-9 in macrophages indicate that macrophages are the main source of MMP-9 in the left ventricle and that they might provide the main inflammatory mechanism of cardiac aging [45].

MOLECULAR GENETIC PREDICTORS OF AGING

Aging can be described as a multifactorial process involving complex interactions between biological and molecular mechanisms [2]. The ability to distinguish between normal biological aging and impaired health is important. There is little experimental evidence in this area. Providing accurate indicators or predictors of ill health, as well as the ability to characterize age-appropriate optimal health, remains an important goal [2].

Aging is a major risk factor for almost all noncommunicable diseases, including cardiovascular diseases, cancer, diabetes, etc. Suggested mechanisms that contribute to aging and the development of these chronic age-related diseases include DNA damage, mitochondrial dysfunction, changes in gene expression and non-coding RNA, genotoxicity, oxidative stress, and telomere shortening [46–48]. It is known that the production of ROS by mitochondria accumulates throughout life, which leads to a state of chronic oxidative stress in old age. Since the mechanisms of antioxidant defense and the ability to repair DNA in the elderly are apparently impaired, DNA damage is considered to be a consequence of aging [49].

Impaired DNA stability is closely associated with age-related diseases. At the age of 60, chromosome lesions cease to accumulate, but in people over 85 years, the frequency of such lesions decreases [50]. Telomeres are shortened due to cell division and oxidative stress and are lengthened due to telomerase and DNA exchange in mitosis. Longer telomeres and higher telomerase activity contribute to genome stability and DNA integrity. Short telomeres are an indicator of oxidative stress and a biomarker of aging [51].

Several genetic pathways are involved in aging. A large number of microRNAs (miRs) are expressed differently during aging [52]. MiRs are found to be stable molecules even in blood serum; therefore, they are considered as promising markers in the clinical setting. Moreover, age and gender can influence the pattern of circulating miRs. [53]. MiRs are also important post-transcriptional regulators of gene expression in skeletal muscle and are associated with aging. MiRs play an important role in age-related changes in mass, composition, and function of skeletal muscles [54, 55].

Blood level of miR-126-3p significantly increases with age. It was significantly higher in the oldest

subjects compared with the youngest healthy subjects (<45 versus >75 years; relative expression: 0.27 ± 0.29 versus 0.48 ± 0.39, $p = 0.047$) [56]. Moreover, some miRs can serve as circulating prognostic biomarkers of cardiovascular aging [57].

PROTEOMIC STUDIES IN VASCULAR AGING

Structural and functional changes occur in aging vessels. They are reflected in the proteome of constituent cell types. Advances in proteomics technologies have made it possible to analyze the amount of proteins associated with the natural history of aortic aging. These changes reflect the molecular and cellular mechanisms of aging and may provide an opportunity to predict vascular health [58]. The characteristics of age-related arterial remodeling include thickening of the aortic wall, increased vascular stiffness, endothelial dysfunction, increased proliferation (invasion and / or secretion of vascular smooth muscle cells), fragmentation of elastic fibers, and collagen deposition.

Proinflammatory arterial remodeling develops with age in both humans and animals. Remodeling leads to changes in the levels of key regulatory proteins involved in pathophysiological processes. The angiotensin II signaling pathway is central in this process. Numerous protein molecules in the angiotensin II signaling pathway are activated and influence vascular remodeling in aging and associated diseases [58].

To identify biomarkers associated with aging, blood samples from 1,890 people aged 18–82 years were analyzed (1,136 men and 754 women) using MALDI-TOF mass spectrometry. The study identified 44 peptides the concentration of which differed in different age groups. The concentration of apolipoprotein A-I (ApoA1) gradually increased between 18 and 50 years of age, the levels of fibrinogen α decreased during the same age period, while albumin significantly degraded in middle-aged people. In addition, the levels of fibrinogen, albumin, and ApoA1 are closely correlated with age [1].

Comparison of young and old rats resulted in the identification of 18 peptides, whose levels vary significantly with age. Analysis of transcription and translation showed that the levels of mRNA and MFG-E8 protein (Milk Fat Globule Protein-Epidermal Growth Factor-8) in the aorta increase with age. Dual immunolabeling shows that MFG-E8 colocalizes with both angiotensin II and monocytic chemoattractant protein-1 in vascular smooth muscle cells of the thickened and aging aortic wall [59].

CONCLUSION

It is known that cardiovascular diseases associated with atherosclerosis are the main cause of morbidity, disability, and mortality in developed countries. Steady aging of the population is considered to be one of the causes of morbidity. The accumulated data indicate that arterial stiffness, arterial wall remodeling, and endothelial dysfunction are independent risk factors for cardiovascular diseases in the elderly. Traditional cardiovascular risk factors, such as high blood pressure, dyslipidemia, obesity, diabetes mellitus, smoking, etc., interact with age-related changes and contribute to the activation of atherosclerotic process. Therefore, in order to prevent the development and growth of cardiovascular diseases in the elderly population, it is necessary to understand the mechanisms underlying age-related pathophysiological changes in blood vessels.

REFERENCES

1. Lu J., Huang Y., Wang Y., Li Y., Zhang Y., Wu J. et al. Profiling plasma peptides for the identification of potential ageing biomarkers in Chinese Han adults. *PLoS One*. 2012;7(7):e39726. DOI: 10.1371/journal.pone.0039726.
2. Wagner K.H., Cameron-Smith D., Wessner B., Franzke B. Biomarkers of Aging: From Function to Molecular Biology. *Nutrients*. 2016;8(6):338. DOI: 10.3390/nu8060338.
3. Laina A., Stellos K., Stamatelopoulos K. Vascular ageing: Underlying mechanisms and clinical implications. *Exp. Gerontol*. 2018;109:16–30. DOI: 10.1016/j.exger.2017.06.007.
4. Sepúlveda C., Palomo I., Fuentes E. Mechanisms of endothelial dysfunction during aging: Predisposition to thrombosis. *Mech. Ageing Dev*. 2017;164:91–99. DOI: 10.1016/j.mad.2017.04.011.
5. Ungvari Z., Tarantini S., Donato A.J., Galvan V., Csiszar A. Mechanisms of vascular aging. *Circ. Res*. 2018;123(7):849–867. DOI: 10.1161/CIRCRESAHA.118.311378.
6. El Assar M., Angulo J., Rodríguez-Mañas L. Oxidative stress and vascular inflammation in aging. *Free Radic. Biol. Med*. 2013;65:380–401. DOI: 10.1016/j.freeradbiomed.2013.07.003.
7. Tan B.L., Norhaizan M.E. Carotenoids: How effective are they to prevent age-related diseases? *Molecules*. 2019;24(9):1801. DOI: 10.3390/molecules24091801.
8. Meschiari C.A., Ero O.K., Pan H., Finkel T., Lindsey M.L. The impact of aging on cardiac extracellular matrix. *GeroScience*. 2017; 39(1):7–18. DOI: 10.1007/s11357-017-9959-9.
9. Wang M., Jiang L., Monticone R.E., Lakatta E.G. Proinflammation: the key to arterial aging. *Trends Endocrinol. Metab*. 2014;25(2):72–79. DOI: 10.1016/j.tem.2013.10.002.
10. Donato A.J., Machin D.R., Lesniewski L.A. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. *Circ. Res*. 2018;123(7):825–848. DOI: 10.1161/CIRCRESAHA.118.312563.
11. Jia G., Aroor A.R., Jia C., Sowers J.R. Endothelial cell senescence in aging-related vascular dysfunction. *Biochim. Bio-*

phys. Acta Mol. Basis. Dis. 2019;1865(7):1802–1809. DOI: 10.1016/j.bbadis.2018.08.008.
12. Rossman M.J., LaRocca T.J., Martens C.R., Seals D.R. Healthy lifestyle-based approaches for successful vascular aging. *J. Appl. Physiol.* 2018;125(6):1888–1900. DOI: 10.1152/japplphysiol.00521.2018.
13. Giudetti A.M., Salzet M., Cassano T. Oxidative stress in aging brain: nutritional and pharmacological interventions for neurodegenerative disorders. *Oxid. Med. Cell Longev*. 2018;2018:3416028. DOI: 10.1155/2018/3416028.
14. Liu Z., Zhou T., Ziegler A.C., Dimitrion P., Zuo L. Oxidative stress in neurodegenerative diseases: from molecular mechanisms to clinical applications. *Oxid. Med. Cell Longev*. 2017;2017:2525967. DOI: 10.1155/2017/2525967
15. Park S., Lakatta E.G. Role of inflammation in the pathogenesis of arterial stiffness. *Yonsei Med. J*. 2012;53(2):258–261. DOI: 10.3349/ymj.2012.53.2.258.
16. Feldman N., Rotter-Maskowitz A., Okun E. DAMPs as mediators of sterile inflammation in aging-related pathologies. *Ageing Res. Rev*. 2015;24(Pt.A):29–39. DOI: 10.1016/j.arr.2015.01.003.
17. Michaud M., Balardy L., Moulis G., Gaudin C., Peyrot C., Vellas B. et al. Proinflammatory cytokines, aging, and age-related diseases. *J. Am. Med. Dir. Assoc*. 2013;14(12):877–882. DOI: 10.1016/j.jamda.2013.05.009.
18. Shaw A.C., Goldstein D.R., Montgomery R.R. Age-dependent dysregulation of innate immunity. *Nat. Rev. Immunol*. 2013;13(12):875–887. DOI: 10.1038/nri3547.
19. Tuttle C.S.L., Thang L.A.N., Maier A.B. Markers of inflammation and their association with muscle strength and mass: A systematic review and meta-analysis. *Ageing Res. Rev*. 2020;64:101185. DOI: 10.1016/j.arr.2020.101185.
20. Visser M., Pahor M., Taaffe D.R., Goodpaster B.H., Simonsick E.M., Newman A.B. et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J. Gerontol. A. Biol. Sci. Med. Sci*. 2002;57(5):M326–332. DOI: 10.1093/gerona/57.5.m326.
21. Kaptoge S., Di Angelantonio E., Lowe G., Pepys MB., Thompson S.G., Collins R. et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet.* 2010;375(9709):132–140. DOI: 10.1016/S0140-6736(09)61717-7.
22. Kabagambe E.K., Judd S.E., Howard V.J., Zakai N.A., Jenny N.S., Hsieh M. et al. Inflammation biomarkers and risk of all-cause mortality in the reasons for geographic and racial differences in stroke cohort. *Am. J. Epidemiol*. 2011;174(3):284–292. DOI: 10.1093/aje/kwr085.
23. Cohen A.A., Milot E., Li Q., Bergeron P., Poirier R., Dusseault-Bélanger F. et al. Detection of a novel, integrative aging process suggests complex physiological integration. *PLoS One*. 2015;10(3):e0116489. DOI: 10.1371/journal.pone.0116489
24. Arai Y., Martin-Ruiz C.M., Takayama M., Abe Y., Takebayashi T., Koyasu S. et al. Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians. *EBioMedicine*. 2015;2(10):1549–1558. DOI: 10.1016/j.ebiom.2015.07.029.
25. Salvioli S., Capri M., Bucci L., Lanni C., Racchi M., Uberti D. et al. Why do centenarians escape or postpone cancer? The role of IGF-1, inflammation and p53. *Cancer Immunol. Immunother*. 2009;58(12):1909–1917. DOI: 10.1007/s00262-008-0639-6.
26. Ragino Y.I., Stakhneva E.M., Polonskaya Y.V., Kashtanova E.V. The role of secretory activity molecules of visceral adipocytes in abdominal obesity in the development of cardiovascular disease: a review. *Biomolecules.* 2020; 10(3):374–392. DOI:10.3390/biom10030374.
27. Gulcelik N.E., Halil M., Ariogul S., Usman A. Adipocytokines and aging: adiponectin and leptin. *Minerva Endocrinol*. 2013;38(2):203–210.
28. Poehls J., Wassel C.L., Harris T.B., Havel P.J., Swarbrick M.M., Cummings S.R. et al. Health ABC Study. Association of adiponectin with mortality in older adults: the Health, Aging, and Body Composition Study. *Diabetologia.* 2009;52(4):591–595. DOI: 10.1007/s00125-009-1261-7.
29. Kistorp C., Raymond I., Pedersen F., Gustafsson F., Faber J., Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005;293(13):1609–1616. DOI: 10.1001/jama.293.13.1609.
30. Nadrowski P., Chudek J., Grodzicki T., Mossakowska M., Skrzypek M., Wiecek A. et al. Plasma level of N-terminal pro brain natriuretic peptide (NT-proBNP) in elderly population in Poland--the PolSenior Study. *Exp. Gerontol*. 2013;48(9):852–857. DOI: 10.1016/j.exger.2013.05.060.
31. Clerico A., Fortunato A., Ripoli A., Prontera C., Zucchelli G.C., Emdin M. Distribution of plasma cardiac troponin I values in healthy subjects: pathophysiological considerations. *Clin. Chem. Lab. Med.* 2008;46(6):804–808. DOI: 10.1515/CCLM.2008.162.
32. Harvey A., Montezano A.C., Lopes R.A., Rios F., Touyz R.M. Vascular fibrosis in aging and hypertension: molecular mechanisms and clinical implications. *Can. J. Cardiol*. 2016;32(5):659–668. DOI: 10.1016/j.cjca.2016.02.070.
33. Nilsson P.M., Boutouyrie P., Cunha P., Kotsis V., Narkiewicz K., Parati G. et al. Early vascular ageing in translation: from laboratory investigations to clinical applications in cardiovascular prevention. *J. Hypertens.* 2013;31(8):1517–1526. DOI: 10.1097/HJH.0b013e328361e4bd.
34. Nilsson P.M. Early vascular aging in hypertension. *Front. Cardiovasc. Med.* 2020;7:6. DOI: 10.3389/fcvm.2020.00006.
35. Wang M., Kim S.H., Monticone R.E., Lakatta E.G. Matrix metalloproteinases promote arterial remodeling in aging, hypertension, and atherosclerosis. *Hypertension*. 2015;65(4):698–703. DOI: 10.1161/HYPERTENSIONAHA.114.03618.
36. Carrick-Ranson G., Spinale F.G., Bhella P.S., Sarma S., Shibata S., Fujimoto N. et al. Plasma matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs and aging and lifelong exercise adaptations in ventricular and arterial stiffness. *Exp. Gerontol*. 2019;123:36–44. DOI: 10.1016/j.exger.2019.05.004.
37. Panwar P., Butler G.S., Jamroz A., Azizi P., Overall C.M., Brömme D. Aging-associated modifications of collagen affect its degradation by matrix metalloproteinases. *Matrix. Biol*. 2018;65:30–44. DOI: 10.1016/j.matbio.2017.06.004.

38. Struewing I.T., Durham S.N., Barnett C.D., Mao C.D. Enhanced endothelial cell senescence by lithium-induced matrix metalloproteinase-1 expression. *The Journal of Biological Chemistry*. 2009; 284(26):17595–17606. DOI: 10.1074/jbc.M109.001735.
39. Myasoedova E.I. The content of matrix metalloproteinase-1 and its inhibitor in patients with ischemic cardiomyopathy. *Journal of New Medical Technologies*. 2016;23(4):50–53 (in Russ.). DOI: 10.12737/23850.
40. Shapiro S., Khodalev O., Bitterman H., Auslender R., Lahat N. Different activation forms of mmp-2 oppositely affect the fate of endothelial cells. American journal of physiology. *Cell Physiology*. 2010;298(4):C942–951. DOI: 10.1152/ajpcell.00305.2009.
41. Momi S., Falcinelli E., Giannini S., Ruggeri L., Cecchetti L., Corazzi T. et al. Loss of matrix metalloproteinase 2 in platelets reduces arterial thrombosis in vivo. *The Journal of Experimental Medicine.* 2009; 206(11):2365–2379. DOI: 10.1084/jem.20090687.
42. Kollarova M., Puzserova A., Balis P., Radosinska D., Tothova L., Bartekova M. et al. Age- and phenotype-dependent changes in circulating MMP-2 and MMP-9 activities in normotensive and hypertensive rats. *Int. J. Mol. Sci*. 2020;21(19):7286. DOI: 10.3390/ijms21197286.
43. Cancemi P., Aiello A., Accardi G., Caldarella R., Candore G., Caruso C. et al. The role of matrix metalloproteinases (MMP-2 and MMP-9) in ageing and longevity: focus on sicilian long-living individuals (LLIs). *Mediators Inflamm*. 2020;2020:8635158. DOI: 10.1155/2020/8635158.
44. Iyer R.P., Chiao Y.A., Flynn E.R., Hakala K., Cates C.A., Weintraub S.T. et al. Matrix metalloproteinase-9- dependent mechanisms of reduced contractility and increased stiffness in the aging heart. *Proteomics Clin. Appl*. 2016;10(1):92–107. DOI:10.1002/prca.201500038.
45. Chiao Y.A., Dai Q., Zhang J., Lin J., Lopez E.F., Ahuja S.S et al. Multi-analyte profiling reveals matrix metalloproteinase-9 and monocyte chemotactic protein-1 as plasma biomarkers of cardiac aging. *Circ. Cardiovasc. Genet*. 2011;4(4):455–462. DOI: 10.1161/CIRCGENETICS.111.959981.
46. Franzke B., Neubauer O., Wagner K.H. Super DNAging-New insights into DNA integrity, genome stability and telomeres in the oldest old. *Mutat. Res. Rev. Mutat. Res*. 2015;766:48–57. DOI: 10.1016/j.mrrev.2015.08.001.
47. Lovell M.A., Markesbery W.R. Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. *Nucleic. Acids Res*. 2007;35(22):7497–7504. DOI: 10.1093/nar/gkm821.
48. Martin-Ruiz C., Dickinson H.O., Keys B., Rowan E., Kenny R.A., Von Zglinicki T. Telomere length predicts poststroke mortality, dementia, and cognitive decline. *Ann. Neurol*. 2006;60(2):174–180. DOI: 10.1002/ana.20869.
49. Hazane F., Sauvaigo S., Douki T., Favier A., Beani J.C. Age-dependent DNA repair and cell cycle distribution of human skin fibroblasts in response to UVA irradiation. *J. Photochem. Photobiol. B.* 2006;82(3):214–223. DOI: 10.1016/j.jphotobiol.2005.10.004.
50. Franzke B., Halper B., Hofmann M., Oesen S., Peherstorfer H., Krejci K. et al. Vienna Active Ageing Study Group. The influence of age and aerobic fitness on chromosomal damage in Austrian institutionalised elderly. *Mutagenesis*. 2014;29(6):441–445. DOI: 10.1093/mutage/geu042.
51. Sanders J.L., Newman A.B. Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? *Epidemiol. Rev*. 2013;35(1):112–131. DOI: 10.1093/epirev/mxs008.
52. Inukai S., Slack F. MicroRNAs and the genetic network in aging. *J. Mol. Biol*. 2013;425(19):3601–3608. DOI: 10.1016/j.jmb.2013.01.023.
53. Keller A., Meese E. Can circulating miRNAs live up to the promise of being minimal invasive biomarkers in clinical settings? *Wiley Interdiscip. Rev. RNA*. 2016;7(2):148–156. DOI: 10.1002/wrna.1320
54. López-Otín C., Blasco M.A., Partridge L., Serrano M., Kroemer G. The hallmarks of aging. *Cell.* 2013;153(6):1194–1217. DOI: 10.1016/j.cell.2013.05.039.
55. McGregor R.A., Poppitt S.D., Cameron-Smith D. Role of microRNAs in the age-related changes in skeletal muscle and diet or exercise interventions to promote healthy aging in humans. *Ageing Res. Rev*. 2014;17:25–33. DOI: 10.1016/j.arr.2014.05.001.
56. Olivieri F., Bonafè M., Spazzafumo L., Gobbi M., Prattichizzo F., Recchioni R. et al. Age- and glycemia-related miR-126-3p levels in plasma and endothelial cells. *Aging (Albany NY)*. 2014;6(9):771–787. DOI: 10.18632/aging.100693.
57. Seeger T., Boon R.A. MicroRNAs in cardiovascular ageing. *J. Physiol*. 2016;594(8):2085–2094. DOI: 10.1113/JP270557.
58. Fu Z., Wang M., Everett A., Lakatta E., Van Eyk J. Can proteomics yield insight into aging aorta? *Proteomics Clin. Appl*. 2013;7(7–8):477–489. DOI: 10.1002/prca.201200138.
59. Fu Z., Wang M., Gucek M., Zhang J., Wu J., Jiang L. et al. Milk fat globule protein epidermal growth factor-8: a pivotal relay element within the angiotensin II and monocyte chemoattractant protein-1 signaling cascade mediating vascular smooth muscle cells invasion. *Circ. Res.* 2009;104(12):1337–1346. DOI: 10.1161/CIRCRESAHA.108.187088.

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