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Different Molecular Pathways of Cardiovascular Aging

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Abstract

Aging is an inevitable process that affects every living organism. It is a body's response to a variety of stressors and is connected to many chronic diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), cardiovascular disease… The aim of this review was to further comprehend the mechanisms of aging process and its effect on cardiovascular system. For collecting sufficient data, different scientific databases were used. In the end, there is no exact conclusion of exactly what causes aging, instead we have different theories of its molecular origins such as: oxidative stress, general wear-and-tear and genetic instability, mitochondrial genome damage, telomere shortening, genetic aging programs… Aging process, especially oxidative stress plays a major role in the pathophysiology of cardiomyocyte senescence. Biological compounds like MicroRNAs, SIR1 gene, NF-κB and IL-4, P66Shc, AMP-activated kinase (AMPK) has also been shown to participate or conduct molecular pathways that take part in aging process as well.

Keywords: aging heart, cardiovascular aging, senescence, molecular pathways

Introduction

Aging is a biological process that results in a progressive and irreversible decline in physical function. It is caused by the accumulation of damage in response to a variety of stressors (Guo J et al., 2022) .The life expectancy itself, is not characteristic of any species, but of populations (Gilbert SF, 2000). That means that although maximum human lifespan is estimated to be 122 (Blagosklonny MV, 2021) , a person can not expect to live for 122 years. In different biological organisms various factors can facilitate or decline aging process. For instance light intensity affects growth rate and lifespan of Drosophila (Northrop JH, 1925), caloric restriction has also been found to impact age-related pathologies in mice and rats (McCay CM et al., 1975), aging in mammals can be slowed by caloric restriction (Lee CK et al., 1999). But the question of exactly what causes aging process is still debated. Perhaps the most

reasonable curse of action would be to look at it at cellular level of organization. But even than different theories emerge such as : oxidative stress, general wear-and-tear and genetic instability, mitochondrial genome damage, telomere shortening, genetic aging programs (Gilbert SF, 2000), loss of proteostasis, histone modification, deregulation of nutrient sensing (Lopez-Otin et al., 2013). Correlation between aging and many chronic illnesses is frequent such as Alzheimer's disease (AD), Parkinson's disease (PD), cardiovascular disease, chronic obstructive pulmonary disease (COPD), osteoporosis (OP… (Guo J et al., 2022).

Globally, cardiovascular diseases (CVDs) is the leading cause of mortality and disability among the growing population of older adults (Tsao CW et al., 2022). Aging process, especially oxidative stress plays a major role in the pathophysiology of cardiomyocyte senescence, hypertrophic remodeling and HF. Increased ROS (oxygen-containing reactive species) levels lead to irreversible cardiomyocyte damage, senescence and death by: contributing to DNA and protein oxidative damage, lipid peroxidation, mitochondrial dysfunction, and cytochrome c release which are strongly associated with severe cardiac dysfunction and HF (heart faillur) progression (Weissman D et al., 2021), several reports have also suggested that oxidative stress in cardiomyocytes induces the premature senescence of cardiac stromal cells, increases the recruitment of CCR2+ monocytes, and eventually contributes to an excessive inflammatory response and cardiac dysfunction (Martini H et al., 2021), but is should be noted that the aging heart phenotype in both , in healthy individuals and patients with coronary vascular disease (CVD) reflects modifications at the cellular level.

Materials and Methods

In order to collect comprehensive and reliable data sources like PubMed, Elsevier, and Google Scholar were searched for articles published between 1945-2024. Keywords like vascular aging, heart disease, rapid aging process were used for finding information. In the investigation Full text articles, reviews, meta analysis and original studies were included. Publications were selected and thoroughly inspected based on the relevance to the subject.

The Aging Heart

Aging is associated with general cardiovascular risk factors, ischemic heart diseases, heart failure, arrhythmias, and cardiomyopathies. It is presented with a significant prevalence in older people. It is also associated with an increase in the frequency of left ventricular (LV) hypertrophy and atrial fibrilation, as well as a decline in diastolic function, and in its exercise capacity despite relatively preserved systolic function at rest (Lakatta, E.G. et al., 2003).

MicroRNAs

Aging remains an independent risk factor itself. It includes many molecular pathways that regulate cardiac and general changes in a body, such as MicroRNAs. MiRNAs are a class of non-coding RNAs that are endogenously expressed and can regulate gene expression on a posttranscriptional level (Bink DI et al., 2023). Aging is specifically associated with an increased

expression of miR-34a, which is caused by an upregulation of p53 signaling and apoptosis (Seeger T et al., 2015).

miR-92a is found in extracellular vesicles of coronary artery patients. Via this pathway, ECs (endothelial cells) receive the miRNA and increase proliferation, migration and therefore angiogenesis via THBS1 witch is an adhesive glycoprotein that plays a role in platelet aggregation and angiogenesis. miR-92a is also upregulated in senescent HUVECs, but it leads to inhibition of oxidative stress, apoptosis and inflammation (Liu H et al., 2017).

NRF2 miR-21 OE was also shown to promote cardiac fibrosis via STAT3 by decreasing CADM1 expression. This leads to the assumption that miR-21 is also an important signaling molecule for cardiac remodeling, it also stimulates proliferation and angiogenesis of endothelial progenitor cells (Dellago H et al., 2013).

miR-100 (hsa-miR-100) is inversely correlated with inflammatory cell content in the lesions, it is discovered to be upregulated in atherosclerotic lesions and suppresses few endothelial adhesion molecules and stimulates EC autophagy. miR-100 OE results in impaired leucocyte-endothelial interaction and is involved in apoptosis, inflammation, and oxidative stress regulation (Pankratz F et al., 2018)

miR-221 and miR-222 (hsa-miR-221/222-3p/5p) have been shown to play a role in promoting proliferation of different cancer cells, they upregulate in senescent ECs (endothelial cells) and both miRNAs suppress eNOS (nitric oxide synthase) expression.

miR-126 causes downregulated in senescent ECs. This decrease in expression leads to impaired tube formation and delayed wound healing abilities, as well as decreased migration, proliferation and angiogenesis (Bink DI et al., 2023).

SIR1

SIRT1 gene, is an NAD-dependent protein (Ellahi A et al., 2016). It has life prolonging properties and various beneficial effects against age-related diseases ranging from metabolic disturbances, such as obesity, diabetes mellitus (especially type 2), cardiovascular, neurodegenerative, pulmonary, renal, musculoskeletal, autoimmune, and skin diseases to cancer. SIRT1 is able to regulate DNA stability and repair, cell death, proliferation and differentiation, mitochondrial biogenesis and function, autophagy, and circadian rhythm, by targeting proteins like H3K9, H4K16, and H1K26, p53, forkhead box protein O1/3 (FOXO1/3), peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), 5′ AMP-activated protein kinase (AMPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Period (Per) 1 and 2, and cryptochrome (Cry), (Sousa C et al., 2022). So it is not a surprise that disfunction of the SIRT1-LKB1-AMPK pathway causes an energy imbalance, cellular stress, and activation of apoptosis mechanisms, which can in the end lead to vascular aging (Pillarisetti S. 2008).

NF-κB and IL-4

IL-34 (interleikin 24) sustains NF-κB pathway activation to increased CCL2 expression, which takes part in macrophage

recruitment and polarization. IL-34 deficiency represses the NF-κB signaling pathway, leading to marked reduction of P-IKKβ and P-IκBα kinase levels; downregulation of NF-κB p65, RelB, and p52 expression, leads to the decline in chemokine CCL2 expression (Zhuang L et al., 2023).

P66Shc

Reactive oxygen species (ROS) have been suggested to play a role in the development of RV hypertrophy (RVH) and the transition to RVF. The hydrogen peroxide-generating protein p66shc has been associated with left ventricular (LV) hypertrophy but its role in RVH is unclear (Hirschhäuser C, et al., 2020).

Dysfunctional endothelium is an early change in vasculature. Among many regulators of vascular endothelial function, p66Shc has been shown to mediate endothelial dysfunction (Kumar S. 2019). In 2019 study was conducted, according of witch. The p66Shc −/− mice are resistant to oxidative stress and have increased lifespan. Judging the vascular endothelial function in the aged p66Shc−/− mice showed that these mice are protected against the aging-induced endothelial dysfunction, increase in inducible-NO (iNOS), superoxide production and reduction in NO bioavailability (Francia P et al., 2004).

AMPK

AMP-activated kinase (AMPK) is a highly conserved sensor of increased levels of AMP (Adenosine monophosphate) and ADP (Adenosine diphosphate) originating from ATP (Adenosine triphosphate) depletion. It controls the autophagic degradation and severity of cellular stress resistance, as well as, integrated signaling network which has a immense role in the regulation of the aging process. .AMPK induced stimulation of FoxO/DAF-16, Nrf2/SKN-1,p53 and SIRT1 signaling pathways improves cellular stress resistance. also, inhibition of NF-κB signaling by AMPK suppresses inflammatory responses. But the ability of AMPK to suppress NF-κB signaling is declined with aging. Studies indicate that the responsiveness of AMPK signaling clearly decrise with aging. The loss of sensitivity of AMPK activation to cellular stress impairs metabolic regulation, increases oxidative stress and reduces autophagic clearance. These age-related changes activate innate immunity defence, triggering a low-grade inflammation and metabolic disorders (Salminen A et al., 2012)

Results

During this review 25 different articles were used, illustrating information about general aging molecular pathways and its effects on cardiovascular system. In the end it became apparent that there is no singular theory that describes how this process works, but the complex of different molecular pathways that still require deeper investigation.

Discussion

Cardiovascular disorders of the aging heart are common problems. Aging process itself is affected by biological and genetic factors in the body such as: oxidative stress, general wear-and-tear and genetic instability, mitochondrial genome damage, telomere shortening, genetic aging

programs loss of proteostasis, histone modification, deregulation of nutrient sensing, epigenetic transcriptome modifications by microRNAs… although compared to the previous years life expectancy of the humans is prolonged, current information about this topic is not complete and there are still many details to be studied. The mechanism and the molecular pathways of the aging process still requires further investigation.

References

1. Bink DI, Pauli J, Maegdefessel L, Boon RA. Endothelial microRNAs and long noncoding RNAs in cardiovascular ageing. Atherosclerosis. 2023 Jun;374:99-106. doi: 10.1016/j.atherosclerosis.2023.03.019. Epub 2023 Apr 5. PMID: 37059656.

2. Blagosklonny MV. No limit to maximal lifespan in humans: how to beat a 122-year-old record. Oncoscience. 2021 Dec 1;8:110-119. doi: 10.18632/oncoscience.547. PMID: 34869788; PMCID: PMC8636159.

3. Dellago H, Preschitz-Kammerhofer B, Terlecki-Zaniewicz L, Schreiner C, Fortschegger K, Chang MW, Hackl M, Monteforte R, Kühnel H, Schosserer M, Gruber F, Tschachler E, Scheideler M, Grillari-Voglauer R, Grillari J, Wieser M. High levels of oncomiR-21 contribute to the senescence-induced growth arrest in normal human cells and its knock-down increases the replicative lifespan. Aging Cell. 2013 Jun;12(3):446-58. doi: 10.1111/acel.12069. Epub 2013 Apr 19. PMID: 23496142; PMCID: PMC3864473.

4. Ellahi A, Rine J. Evolution and Functional Trajectory of Sir1 in Gene Silencing. Mol Cell Biol. 2016 Jan 25;36(7):1164-79. doi: 10.1128/MCB.01013-15. PMID: 26811328; PMCID: PMC4800792.

5. Francia P, delli Gatti C, Bachschmid M, Martin-Padura I, Savoia C, Migliaccio E, Pelicci PG, Schiavoni M, Lüscher TF, Volpe M, Cosentino F. Deletion of p66shc gene protects against age-related endothelial dysfunction. Circulation. 2004 Nov 2;110(18):2889-95. doi: 10.1161/01.CIR.0000147731.24444.4D. Epub 2004 Oct 25. PMID: 15505103.

6. Gilbert SF. Developmental Biology. 6th edition. Sunderland (MA): Sinauer Associates; 2000. Aging: The Biology of Senescence. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10041/

7. Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, Li J. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther. 2022 Dec 16;7(1):391. doi: 10.1038/s41392-022-01251-0. PMID: 36522308; PMCID: PMC9755275.

8. Hirschhäuser C, Sydykov A, Wolf A, Esfandiary A, Bornbaum J, Kutsche HS, Boengler K, Sommer N, Schreckenberg R, Schlüter KD, Weissmann N, Schermuly R, Schulz R. Lack of Contribution of p66shc to Pressure Overload-Induced Right Heart Hypertrophy. Int J Mol Sci. 2020 Dec 8;21(24):9339. doi: 10.3390/ijms21249339. PMID: 33302436; PMCID: PMC7762598.

9. Kumar S. P66Shc and vascular endothelial function. Biosci Rep. 2019 Apr 30;39(4):BSR20182134. doi: 10.1042/BSR20182134. PMID: 30918103; PMCID: PMC6488855.

10. Lakatta, E.G.; Levy, D. Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises: Part II: The aging heart in health: Links to heart disease. Circulation 2003, 107, 346–354

11. Lee CK, Klopp RG, Weindruch R, Prolla TA. Gene expression profile of aging and its

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retardation by caloric restriction. Science. 1999 Aug 27;285(5432):1390-3. doi: 10.1126/science.285.5432.1390. PMID: 10464095.
12. Liu H, Wu HY, Wang WY, Zhao ZL, Liu XY, Wang LY. Regulation of miR-92a on vascular endothelial aging via mediating Nrf2-KEAP1-ARE signal pathway. Eur Rev Med Pharmacol Sci. 2017 Jun;21(11):2734-2742. PMID: 28678311.
13. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153:1194–1217. doi: 10.1016/j.cell.2013.05.039.
14. Martini H, Lefevre L, Sayir S, Itier R, Maggiorani D, Dutaur M, Marsal DJ, Roncalli J, Pizzinat N, Cussac D, Parini A, Mialet-Perez J, Douin-Echinard V. Selective Cardiomyocyte Oxidative Stress Leads to Bystander Senescence of Cardiac Stromal Cells. Int J Mol Sci. 2021 Feb 24;22(5):2245. doi: 10.3390/ijms22052245. PMID: 33668142; PMCID: PMC7956294.
15. McCay CM, Maynard LA, Sperling G, Barnes LL. The Journal of Nutrition. Volume 18 July--December, 1939. Pages 1--13. Retarded growth, life span, ultimate body size and age changes in the albino rat after feeding diets restricted in calories. Nutr Rev. 1975 Aug;33(8):241-3. doi: 10.1111/j.1753-4887.1975.tb05227.x. PMID: 1095975
16. Moore KJ, Rayner KJ. Local Anti-miR Delivery: The Latest in the Arsenal of Drug-Eluting Stents. Arterioscler Thromb Vasc Biol. 2015 Sep;35(9):1905-6. doi: 10.1161/ATVBAHA.115.306187. PMID: 26310808; PMCID: PMC4617631.
17. Pankratz F, Hohnloser C, Bemtgen X, Jaenich C, Kreuzaler S, Hoefer I, Pasterkamp G, Mastroianni J, Zeiser R, Smolka C, Schneider L, Martin J, Juschkat M, Helbing T, Moser M, Bode C, Grundmann S. MicroRNA-100 Suppresses Chronic Vascular Inflammation by Stimulation of Endothelial Autophagy. Circ Res. 2018 Feb 2;122(3):417-432. doi: 10.1161/CIRCRESAHA.117.311428. Epub 2017 Dec 5. PMID: 29208678.
18. Pillarisetti S. A review of Sirt1 and Sirt1 modulators in cardiovascular and metabolic diseases. Recent Pat Cardiovasc Drug Discov. 2008 Nov;3(3):156-64. doi: 10.2174/157489008786263989. PMID: 18991791.
19. Salminen A, Kaarniranta K. AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network. Ageing Res Rev. 2012 Apr;11(2):230-41. doi: 10.1016/j.arr.2011.12.005. Epub 2011 Dec 15. PMID: 22186033.
20. Seeger T, Boon RA. MicroRNAs in cardiovascular ageing. J Physiol. 2016 Apr 15;594(8):2085-94. doi: 10.1113/JP270557. Epub 2015 Jul 5. PMID: 26040259; PMCID: PMC4933109.
21. Sousa C, Mendes AF. Monoterpenes as Sirtuin-1 Activators: Therapeutic Potential in Aging and Related Diseases. Biomolecules. 2022 Jun 30;12(7):921. doi: 10.3390/biom12070921. PMID: 35883477; PMCID: PMC9313249.
22. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Ferguson JF, Generoso G, Ho JE, Kalani R, Khan SS, Kissela BM, Knutson KL, Levine DA, Lewis TT, Liu J, Loop MS, Ma J, Mussolino ME, Navaneethan SD, Perak AM, Poudel R, Rezk-Hanna M, Roth GA, Schroeder EB, Shah SH, Thacker EL, VanWagner LB, Virani SS, Voecks JH, Wang NY, Yaffe K, Martin SS. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation.

2022 Feb 22;145(8):e153-e639. doi: 10.1161/CIR.0000000000001052. Epub 2022 Jan 26. Erratum in: Circulation. 2022 Sep 6;146(10):e141. doi: 10.1161/CIR.0000000000001074. PMID: 35078371.
23. Wang LL, Liu Y, Chung JJ, Wang T, Gaffey AC, Lu M, Cavanaugh CA, Zhou S, Kanade R, Atluri P, Morrisey EE, Burdick JA. Local and sustained miRNA delivery from an injectable hydrogel promotes cardiomyocyte proliferation and functional regeneration after ischemic injury. Nat Biomed Eng. 2017;1:983-992. doi: 10.1038/s41551-017-0157-y. Epub 2017 Nov 27. PMID: 29354322; PMCID: PMC5773070.
24. Weissman D, Maack C. Redox signaling in heart failure and therapeutic implications. Free Radic. Biol. Med. 2021;171:345–364. doi: 10.1016/j.freeradbiomed.2021.05.013.
25. Zhuang L, Zong X, Yang Q, Fan Q, Tao R. Interleukin-34-NF-κB signaling aggravates myocardial ischemic/reperfusion injury by facilitating macrophage recruitment and polarization. EBioMedicine. 2023 Sep;95:104744. doi: 10.1016/j.ebiom.2023.104744. Epub 2023 Aug 8. PMID: 37556943; PMCID: PMC10433018.

