INVITED REVIEW ARTICLE

A PILLAR OF CARDIOVASCULAR DISEASES: INFLAMMAGING

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Abstract

With the prolongation of life expectancy, the increase in the number of elderly individuals in societies and the high rates of disability, frailty and morbidity associated with this situation have led to the acceptance of old age as a prior social problem. And since the 2000s, many studies have been carried out in this field.

Inflammation is a very important physiological function and a complex biological process that is initiated by the immune system in response to infection, injury or tissue damage. In connection with this process, inflammaging refers to the chronic, low-grade inflammation that occurs with aging.

As one ages, the immune system undergoes changes including a descent in the production of new immune cells and a decrease in the ability of existing immune cells to function properly that can contribute to a state of chronic inflammation. Clinical trials suggest that modulating inflammation prevents many of the chronic diseases, frailty, and disability that increases at older age.

In the light of existing information, one can predict that a possible reason for long life today is the capability of reaching an optimal balance between pro-inflammatory (C-Reactive Protein, Interleukin 6, Tumor necrosis factor-alpha) and anti-inflammatory (Interleukin-1 receptor antagonist protein, Cortisol, Interleukin-10) molecules.

Keywords: Aging; Cellular Senescence; Inflammation; Immunosenescence.

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INFLAMMATION

Inflammation is a very important physiological function and a complex biological process that is initiated by the immune system in response to infection,injury or tissue damage. It is a natural and important part of the body's defense mechanism to protect the body from invasion, infection and death resulting with the healing of the damaged tissues, but it can also contribute to various diseases if becomes chronic or aggressive (1).

Tonsils and adenoids, thymus, lymph nodes and vessels, spleen and bone marrow are the major organs that take part in the immune system by secreting macrophage and the T and B cells. Also skin, the endothelium of the digestive and respiratory trucks also act as an important surface barrier for the pathogens.

Acute inflammation is the major part of a cardiovascular surgeons routine daily practice. The perioperative period is a potentially deletirious time because the combination of anesthesia, the stress of surgery, and the immüne stimulation effect of the cardiopulmonary bypass (CPB) circuit result in a systemic inflammatory response (2).

Possible responsible etiologic factors are;

A-Cellular activation with contact of blood products with the surface of the bypass circuit,

B-Mechanical shear stress that occur due to the blood passing through the suction systems and filters,

C-Tissue ischemia and reperfusion,

D-The effect of hypotension and hemodilution,

E-Administration of blood products and

F-Mild to deep hypothermia utilization during the cardiopulmonary bypass.

The effect of surgical trauma and CPB results in complement activation by both classical (protamine related) and alternative (contact with foreign surfaces) pathways.These two pathways result in the elevation of C3a and C5a which lead to activation and degranulation of neutrophils, release of histamine from mast cells, basophills, and platelet aggregation (3).

Cytokines are produced by macrophages, lymphocytes, monocytes, and endothelial cells. These factors are either proinflammatory in the form of IL-6, IL-8 and tumor necrosis factor alpha or antiinflammatory in the form of IL-10, and IL-1 receptor antagonists.

An increase in TNF alpha has been demonstrated with increased capillary leak. Elevations in IL-6 and IL-8 result with increased inotropic requirements, severe capillary leak syndrome, and an increase in mortality.In uncomplicated cases the systemic inflammatory response is self limited and is only of a few days duration but organ dysfunction may occur in those who show an extensive systemic inflammatory response.

As mentioned above in a normal inflammatory reaction when the stress or infection occurs the immüne response begins and IL-6 and CRP release and increase in time. After recovery begins they decrease and immüne reaction ends after complete healing.

INFLAMMAGING

Inflammaging refers to the chronic, low-grade inflammation that occurs with aging. As we age, our immune system undergoes changes including a descent in the production of new immune cells and a decrease in the ability of existing immune cells to function properly that can contribute to a state of chronic inflammation (4).

There is a continuous increase in pro-inflammatory cytokines, a decrease in anti-inflammatory cytokines, and changes in the function of immune cells such as macrophages and T cells. Although the initiating factor deceased or cured dysregulated chronic inflammation continue to progress, and is believed to play a role in many

age-related diseases, including cardiovascular and pulmonary disease, cancer, neurodegenerative, autoimmune,and metabolic disorders and demantia (5, 6).

There has been a significant amount of research conducted on inflammaging in recent years to better understand its mechanisms and potential therapeutic interventions.

The level of proinflamatory markers are at baseline up to approximately 60 to 65 years both in men and woman and then begin to increase continuously due to inflammaging. Inflammatory markers IL 6 and whereas a little bit slower CRP both tend to increase very rapidly. Those who have elevated inflammation not only tend to have more disease, but also become predisposed to have an increase in the number of diseases over the subsequent years (1).

It was shown in 2015 that there is a correlation between the level of IL-6 and the number of illnesses that a patient have.For example at age 70 if you have high baseline IL-6 and faster increase of IL-6 over time, you may have 2 to 3 illnesses where as at age 90 you have more than 4 illnesses if this condition persists (7).

If treatment of the inflammation is effective it ends with healing, but if inflammation continue as in inflammaging sytemic effects occur that not only cause to multiple chronic diseases, but also the geriatric syndromes, like frailty or age-related muscle diseases and loss, as well as decreased physical endurance or decreased ability to respond to a stress, for example to recover after surgery or creating an immune response after vaccination (8, 9).

The results of the study by Ferrucci and Fabbri in 2018 suggested that inflammageing is not-only a risk factor for cardiovascular diseases (CVDs), but is also a risk factor for chronic kidney disease, diabetes mellitus, cancer, depression, dementia, and sarcopenia (10).

Factors that lead to inflammaging:

- Genetic predisposition,
- Visceral and central obesity,
- Increased gut permeability and changes in gut microbiota,
- Mithocondrial dysfunction that lead to oxidative stress,
- Intrinsic immune cells defect,
- Cellular senescence.

Mechanisms

Nowadays inflammaging is considered as a phenomenon that increases the rate of ageing and many chronic diseases that are basically related to age. So these age-related diseases can be considered as the manifestations of accelerated ageing due to inflammaging.

In connection with the genetic background of individuals, environmental factors and lifestyles may accelerate or decelerate the aging process (5).

In brain chronic inflammation activates migroglia and inhibits neurogenesis;at arteries it stimulates atherosclerosis, and inhibit endothelial reactivity; inhibits hematopoesis at bone marrow,stimulates osteoclasts and downregulates osteocalcin;inhibits muscle growth, and in the gastrointestinal system it reduces food absorbtion,and also causes insulin resistance (5, 7, 11).

The two most important mechanisms that are recognized as possible cause of chronic inflammation with aging are the cellular senescence and the increase in intestinal permeability and microbiota change which leads to a loss of protection in this very important barrier.

One of the processes that appears to be contributed to chronic low grade inflammation with aging is cellular senescence which was discovered and named in the early 1960s by observing that normally multiplying cells stop dividing.

Senescent cells are cells that have entered a state of irreversible growth arrest, meaning they no longer divide or function properly. They are especially located in skin and adipose tissue and are usually larger than non-senescent cells. Senescence is a natural process that serves as a protective mechanism to prevent damaged or potentially cancerous cells from continuing to divide and potentially causing progressive harm to the organism, The secretome of senescent cells is a very complex procedure. The products are mainly associated with inflammation, proliferation, and changes in the extracellular matrix. Also they play a pathological role in age-related diseases (4).

However, while senescence can be beneficial in some contexts, accumulated senescent cells over time can contribute to various age-related diseases and the overall aging process. Some senescent cells become very large, have increased protein production, and may exhibit a secretory state where they produce inflammatory mediators, chemokines that attract immune cells, and other factors that damage tissues around them. This chronic inflammation and tissue dysfunction are thought to play a role in age-related diseases (1, 5).

The abundance of senescent cell begins to particularly increase in the ages between 60 and 80. The older individuals have more senescent cells in their fat tissue than the younger individuals. So central and visceral obesity is a major risk factor for inflammaging.

Small numbers of senescent cells, if they're transplanted into younger individuals, can cause an aging like state. It was shown that if you transplant just a million senescent cells into a mouse resulting only one out of 10,000 cells in that mouse is a transplanted senescent cell, this is sufficient to make that mice die earlier of all age-related diseases and they exhibit the signs and markers of inflammation.

So very small numbers of senescent cells are sufficient to cause problems. There's a threshold in the number of senescent cells that will cause problems. Once you exceed that threshold, senescent cells cause senescense in other cells near and at a distance to them.By this way senescent spreads from cell to cell (4,12).

The immune system normally clear senescent cells. Once the rate of formation of new senescent cells exceeds the ability of the immune system to clear them, there will be an exponential increase in their numbers, and start getting age-related disorders and diseases (9).

OBESITY

As another important factor, pro-inflammatory and chemotactic compounds are produced by macrophages, lymphocytes, and senescent cells that are located at the central and visceral fat tissue in obese individuals contributing to inflammaging.

MICROBIATA

Our immune cells, which live in the layer underneath the gut, are constantly sampling inner microbiata in order to make decisions about which are pathogens which needs to be responded to and which are nonharmful organisms that they shouldn't respond to (13).

As the immune system ages, it loses some of this capacity, and ability to monitor and to destroy the harmful microbes. So microbial composition shifts, and this ultimately leads to microbial dysbiosis, or a harmful or unhealthy change in the gut microbiome. This age-related microbial dysbiosis promotes intestinal permeability which allow for the translocation of bacterial products from the gut into the vascular system, and once these products are in the circulation, we have systemic inflammation. Young immune system can clear these products fairly quickly. However, as getting older the systemic inflammation affects the immune cells that are required to keep that gut microbiome under control. Also the ability of macrophages to delete this

harmful bacteria decreases, inflammation continue to increase, and so the visious cycle continues (13, 14).

DIET

Researches show that in developing countries people have a high fat, low fibre diet. They have chronic stress, inactivity, and smoking. All these result in an increase in intestinal permeability and many chronic diseases in a vicious cycle. So the average age of men is 76 and women is 82.Whereas in developed countries people eat low fat, high fibre diet, and have healthy microbiome.The stress is low, they have time to exercise,have safe jobs and safe enviroment. These lead to less intestinal permeability and the mean age is 81 in men and 84 in women (5, 14).

ALVEOLER SYSTEM

The lungs are constantly exposed to environmental pollutants, allergens, and irritants, which can damage the alveoler endothelium and airways during years. As we age, these changes can accelerate, leading to a decline in lung function due to:

- The airways become narrower and less elastic. This makes it harder to breathe in and out.
- The alveoli, where gas exchange takes place, become smaller and less numerous. This reduces the surface area available for gas exchange.
- The muscles that support breathing become weaker which makes it harder to breathe deeply.
- The production of mucus decreases. This can make it more difficult to clear mucus from the airways.
- The immune system in the lungs becomes less effective. This makes it harder to fight off infections.

The same mechanism of impaired integrity of epithelial cells in the lungs, like in the gut leads to increase permeability in the lungs, disorders of mucus secretion and clearence lead to bacterial entrance and inflammation which ends in diseases such as bronchitis, asthma, chronic obstructive pulmonary disease, emphysema, pneumonia and lung cancer (15).

SMOKING

Smoking also lead to oxidative stress and cytokine production which results in inflammaging and induces and aggravates the inflammatory response in the airway that ends in age related respiratory diseases , cardiovascular disease, and cancer One study found that smoking cessation led to a significant reduction in inflammatory markers in older adults.

CARDIOVASCULAR SYSTEM

There are several molecular mechanisms that play role in cardiac and vascular inflammaging (16, 17).

Accumulation of low-density lipoprotein (LDL) cholesterol in the damaged endothelium of the arterial wall tend to be oxidized and triggers an inflammatory response and atherosclerosis begins. The initiation and progression of atherogenesis is contributed by innate and adaptive immunity starting from early endothelial dysfunction to the development of acute thrombotic complications (18). In later stages thrombotic complications can be seen that are triggered by plaque rupture or erosion. Currently, the detailed mechanisms that affect the formation and progression of atherosclerosis cannot yet be fully explained. In this context, it is believed that the different mechanisms involved in the accumulation of inflammatory markers accelerate clinical progression and lead to a vicious cycle. According to the results of researches, regardless of other cardiovascular disease risk factors, high blood pro-inflammatory markers, including high-sensitivity

C-reactive protein (hsCRP) and Interleukin 6 (IL-6) in particular, predict the risk of cardiovascular disease in both middle-aged and older adults (19).

Together with the low-grade systemic inflammation, cardiac aging leads to cardiac inflammation and downregulation of main energy regulating mechanisms, and mitochondrial dysfunction leading to endothelial/myocardial dysfunction. These changes can affect the heart's ability to pump blood and can increase the risk of heart disease,and heart failure (20, 21).

Here are some of the changes that occur in the aging heart due to inflammaging:

- The heart muscle becomes less elastic. This makes it harder for the heart to relax and fill with blood.
- The heart valves become stiffer. This can make it harder for the valves to open and close properly.
- The arteries become narrower and less elastic. This makes it harder for blood to flow through the arteries.
- The endothelium of the blood vessels becomes damaged and more susceptible to inflammation. This can lead to the formation of plaque, which can progressively narrow the vessels and restrict blood flow.
- The conduction system of the heart becomes less efficient. This can lead to arrhythmias, or irregular heart beats.

These changes can lead to a number of heart problems, including:

- Heart failure
- Coronary artery disease
- Arrhythmias
- Stroke
- High blood pressure
- Peripheral arterial disease
- Venous insufficiency

Epicardial adipose tissue (EAT), which covers 80% of the heart surface and accounts for 20% of the total heart weight, is defined as the visceral fat storage of the heart (22).

The inflammatory process that increases during aging is characterized by an increase in the release of inflammatory mediators and neuro-hormones by EAT contributing to development and progression of cardiovascular diseases by directly penetrating through the myocardium and coronary vessels. As the result of expressing their toxicity in the neighboring tissues not only coronary artery disease, but aortic stenosis, atrial fibrillation and even heart failure can be seen.

There are studies supporting the correlation between worse cardiovascular outcome and EAT accumulation. A reliable quantification of EAT is considered to be very important using different imaging techniques such as echocardiography, computerized tomography scan and cardiovascular magnetic resonance imaging in order to explore the potential impact of EAT on the progress of cardiovascular diseases. Coronary artery disease patients having more than 7 mm EAT thickness were considered to have higher risk of myocardial infarction and cardiovascular death by Tanındı et al (23).

Evaluation of EAT thickness can also be useful for predicting intensive care unit complications such as the onset of atrial fibrillation, prolonged inotrope use, and even fever after coronary bypass surgery.

BRAIN

The aging brain undergoes a number of changes that can affect cognitive function, memory, and mood. Some of these changes are:

- Decrease in the brain size and weight: The brain gradually shrinks as we age, starting in our 40s. This is due to the loss of neurons and synapses.

- Accumulation of amyloid plaques which are protein deposits that can build up in the brain and damage neurons. They are associated with Alzheimer's disease and other forms of dementia.
- Chronic inflammation can damage neurons and contribute to cognitive decline, trouble multitasking which is the ability to do two or more things at once. It can become more difficult to do as we age.
- As getting older, the blood vessels that supply the brain with oxygen and nutrients can become narrowed or blocked. This can lead to decrease in blood flow to the brain,and ends in decline in the cognitive function and mood and personality changes including depression, anxiety, and irritability (21).
- Neurotransmitters are chemicals that allow neurons to communicate with each other. As we age, the production of some neurotransmitters, such as acetylcholine, can decrease. This can lead to problems with memory loss and slowed thinking make it difficult to concentrate, learn new things, or make decisions. Memory loss is the most common symptom of aging brain. It can range from mild forgetfulness to difficulty remembering recent events or familiar faces.

EATING HABBIT

It has been shown that nutrient content, amount of food, time of meal and rhythm have a significant effect on intestinal microbiota and metabolism and maintain a basal physiological inflammation level, whereas overnutrition and inflammation may increase with changes in all these (24).

A study was conducted to identify factors influencing intention and behavior of fast-food consumption. A group of people ate fast food like meal where as a second group has eaten healthy meal. And it was shown that IL 6 began to increase in 50 minutes in both groups. But after 8 hours there was a significant increase in the fast food group.

SLEEP

Prolonged sleep deficiencies such as short sleep duration or sleep disturbances, lead to chronic, systemic low-grade inflammation (inflammaging) and is associated with diseases that have an inflammatory component, i.e. diabetes,atherosclerosis, and neurodegeneration (25).

Another research conducted on the correlation of short sleep duration and cardiometabolic risk showed that increased risk of atherosclerosis and hypertension,impaired heart rate variability and increased risk of coronary artery disease ,heart failure and arythmia,increased risk of diabetes mellitus,increased risk of metabolic syndrome and obesity,increased susceptibility to viral infections,irritability,cognitive impairment,memory lapses or loss may occur due to short sleep duration (26).

Overall, lifestyle factors can have a significant impact on inflammaging, with healthy behaviors such as a balanced diet, regular exercise, and adequate sleep helping to reduce chronic inflammation and improve healthy outcomes in older adults.

PREVENTION

There are some basic tips to keep inflammaging low:

- Get a good night's sleep: 7-8 hours sleep duration must be essential and it has been reported that older adults with poor sleep quality had higher levels of inflammatory markers compared to those with good sleep quality. Also deep sleep is important for reducing inflammation and oxidative stress.
- Drink plenty of water

- Eat lots of good veggies and nutrient-rich food; avoid high sugar and low-nutrient dense food: A diet high in processed foods, saturated fats, and sugar has been shown to increase inflammation, while a diet rich in fruits, vegetables, whole grains, and healthy fats, such as omega-3 fatty acids, can reduce inflammation. For example, a study published in the Journal of Nutrition found that a Mediterranean-style diet, which is rich in anti-inflammatory foods, reduced levels of inflammatory markers in older adults.
- Perform regular moderate exercise: Walking 20 minutes daily has been shown to reduce inflammation and slow the aging process. Studies found that older adults who engaged in regular exercise had lower levels of inflammatory markers compared to sedentary adults. Regular exercise can lower levels of pro-inflammatory cytokines and increase anti-inflammatory cytokines, leading to reduced inflammation. Additionally, exercise can also improve cardiovascular health, which is closely linked to inflammaging.
- Finally, stress can also contribute to inflammaging, with chronic stress leading to increased levels of pro-inflammatory cytokines. Relaxation techniques such as meditation and yoga have been shown to reduce stress and inflammation.

POTENTIAL TREATMENT STRATEGIES

There is currently a lot of research on how to target senescent cells in order to prevent and treat age-related diseases. Some potential therapies include:

Medicines designed to selectively kill senescent cells, and aimed at reducing tissue inflammation are named as "senolytic drugs". It has been shown that senolytics delay and prevent the development of many chronic diseases in mice, thus improving their health and quality of life.

Some examples of senolytic drugs that have been studied in preclinical and clinical trials are:

1. Dasatinib and quercetin: This combination of drugs has been shown to selectively eliminate senescent cells in mice and improve cardiovascular function.
2. Navitoclax: It has been shown that navitoclax selectively eliminate senescent cells in atherosclerotic mice and improve vascular function.
3. ABT-263: This drug also has been shown to selectively eliminate senescent cells in mice and improve tissue function.
4. Fisetin: This natural compound has been shown to selectively eliminate senescent cells in mice and improve physical function.
5. Rapamycine
6. Piperlongamine

In animal models the senolytic drugs do not kill the normal cells. It was shown that 30 to 70% of senescent cells are killed by these kind of drugs, and that's roughly correlates with the percentage of senescent cells that are trying to kill other cells and produce inflammatory markers. Also senescent cells take two to six weeks to form again. So these drugs can be given once every couple of weeks or once a month if there's continuing stimulus for new senescent cells to form (27, 28).

The development of effective drugs in this area will prevent chronic inflammation that causes aging, delay human aging, increase the quality of life and thus prolong longevity.

Immunotherapy is an another approach using the immune system to target and kill senescent cell (29).

The development of effective therapies for targeting senescent cells has the potential to revolutionize the way we treat age-related diseases.

Both in preclinical and clinical studies, while evaluating the suitable molecular biomarkers and

pathways, consideration of personal aging should be prioritized. Since there are sex differences in the process of aging and chronic diseases, both genders should be included. And for immunosurveillance, targets should be unique antigens or ligands of senescent cells.

Clinical trials suggest that modulating inflammation prevents many of the chronic diseases, frailty, and disability that increases at older age.

Due to the researches we can estimate that a possible main reason why people reach 100+ are because they are capable of reaching an optimal balance between pro-(CRP, IL-6, TNF alpha) and anti-inflammatory (IL1RA, Cortisol, IL-10) molecules (29, 30).

REFERENCES

1. Ferruci L, Corsi A, Lauretani F, et al. The origins of age-related proinflammatory state. Blood 2005;105 (6): 2294–9. (DOI:10.1182/blood-2004-07-2599).
2. Tang Q, Dong C, Sun Q. Immune response associated with ischemia and reperfusion injury during organ transplantation. Inflammation Research 2022; 71:1463–76. (DOI: 10.1007/s00011-022-01651-6).
3. Kutsal Ali, Ersoy Ü, Ersoy F, et al. Complement Activation During Cardiopulmonary Bypass. The Journal of Cardiovascular Surgery.1989; 30(3): 359-63. (PMID: 2745519).
4. Kirkwood KL. Inflammaging. Immunol Invest 2018:47 (8):770-3. (DOI:10.1080/08820139.2018.1552392).
5. Franchesci C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. Nat Rev Endocrinol 2018; 14:576–90. (DOI:10.1038/s41574-018-0059-4).
6. Liberale L, Badimon L, Montecuccu F, et al. Inflammation, Aging and Cardiovascular Disease: JACC Review Topic of the Week. J Am Coll Cardiol 2022;1;79(8):837- 47. (DOI:10.1016/j.jacc.2021.12.017).
7. Fabbri E, Yang A, Zoli M, et al. Aging and the burden of multimorbidity: associations with inflammatory and anabolic hormonal biomarkers. J Gerontol A Biol Sci Med Sci 2015 Jan;70(1):63-70. (DOI: 10.1093/gerona/glu127).
8. Perrone MA, Aimo A, Bernardini S, Clerico A. Inflammageing and Cardiovascular System: Focus on Cardiokines and Cardiac-Specific Biomarkers. Int J Mol Sci. 2023; 24, 844. (DOI:10.3390/ijms24010844).
9. Sendamaa W.The effect of ageing on the resolution of inflammation. Ageing Research Reviews 2020;57: 101000 1568-1637. (DOI: 10.1016/j.arr.2019.101000).
10. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018, 15(9):505-22. (DOI:10.1038/s41569-018-0064-2).
11. Shakeri H, Lemmens K, Gevaert AB, De Meyer GRY. Segers V. Cellular senescence links aging and diabetes in cardiovascular disease. Am J Physiol, Heart Circ Physiol 2018;10.1152. (DOI:10.1152/ajpheart.00287.2018).
12. Sanada F, Taniyama Y, Muratsu J, et al. Source of ChronicInflammation in Aging. Front Cardiovasc Med 2018; 5:12. (DOI:10.3389/fcvm.2018.00012).
13. Tropini C,Earle KA,Huang KC,Sonnenburg JL.The Gut Microbiome: Connecting Spatial Organization to Function. Cell Host Microbe 2017; 21(12): 433-42. (DOI:10.1016/j.chom.2017.03.010).
14. Thevaranjan N, Puchta A, Schulz C, et al. Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction. Cell Host Microbe 2017; 21, 455-66. (DOI: 10.1016/j.chom.2018.03.006).
15. Shijin X, Changxi Z, Bill K, Shuang Xiaoping, Haiyan G, Wen G. Combined Antioxidant, Anti-inflammaging and Mesenchymal Stem Cell Treatment: A Possible Therapeutic Direction in Elderly Patients with Chronic Obstructive Pulmonary Disease. Aging and disease 2020, 11(1): 129-40. (DOI: 10.14336/AD.2019.0508).
16. Ajoolabady A, Pratico D, Vinciguerra M, et al. Inflammaging: mechanisms and role in the cardiac and vasculature. Trends Endoc Metabol 2023 ;34(6):373- (DOI 10.1016/j.tem.2023.03.005).
17. Koc M, Kutsal A.Vascular Aging. Turkish J Geriatrics 2015;18(2):156-61.
18. Gimbrone MAJ, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ. Res 2016; 118, 620-36. (DOI: 10.1161/CIRCRESAHA.115.306301).
19. Barcena ML, Aslam M, Pozdniakova S, Norman K, Ladilov Y. Cardiovascular Inflammaging: Mechanisms

and Translational Aspects. Cells. 2022; 16;11(6):1010. (DOI:10.3390/cells11061010).

20. Haobo L, Hastings MH, Rhee J, et al. Targeting Age-Related Pathways in Heart Failure. Circulation Research. 2020;126: 533–51. (DOI: 10.1161/CIRCRESAHA.119.315889).
21. Bollini S, Camici GG. Cardiovascular Research Scientists on the Spot: Cardiovascular ageing and stroke 2021; (117,); e169–e170. (DOI:10.1093/cvr/cvab345).
22. Conte M, Petraglia L, Poggio P et al. Inflammation and Cardiovascular Diseases in the Elderly: The Role of Epicardial Adipose Tissue. Front Med (Lausanne) 2022 Feb 15; 9: 844266. (DOI: 10.3389/fmed.2022.844266).
23. Tanındı A, Kocaman SA, Erkan AF, et al. Epicardial adipose tissue thickness is associated with myocardial infarction and impaired coronary perfusion. Anatol J Cardiol. 2015 Mar;15(3):224-31. (DOI: 10.5152/akd.2014.5277).
24. SM Friedman. The Interface Between Healthy Aging, Longevity, Disease, and Disability. In: Coll, P. (Eds) Healthy Aging. Springer, Cham. Switzerland AG 2019, pp:23-9.
25. Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. Physiol Rev. 2019 1;99(3):1325-1380. (DOI: 10.1152/physrev.00010.2018).
26. Tobaldini E, Fiorelli EM, Solbiati M, Costantino G, Nobili L, Montano N. Short sleep duration and cardiometabolic risk: from pathophysiology to clinical evidence. Nat Rev Cardiol. 2019; 16(4):213-24. (DOI: 10.1038/s41569-018-0109-6).
27. Iske J, Seyda M, Heinbokel T, et al. Senolytics prevent mt-DNA-induced inflammation and promote the survival of aged organs following transplantation.Nature Communications. 2020;11: 4289. (DOI:10.1038/s41467-020-18039-x).
28. Sun Y, Li Q, Kirkland JL. Targeting senescent cells for a healthier longevity: the roadmap for an era of global aging. Life Medicine, 2022;1:103–19. (DOI:10.1093/lifemedi/lnac030).
29. Song P, An J, Zou MH. Immune Clearance of Senescent Cells to Combat Ageing and Chronic Diseases. Cells. 2020 Mar 10;9(3):671. (DOI: 10.3390/cells9030671).
30. Libby P Interleukin-1 β as a target for atherosclerosis therapy: biological basis of CANTOS and beyond. J. Am. Coll. Cardiol 2017;70, 2278–89. (DOI: 10.1016/j.jacc.2017.09.028).