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Biomarkers of aging-associated chronic inflammation as a prognostic factor for human longevity

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Abstract

It has been well-established that age-associated low-grade chronic inflammation contributes to the development of a spectrum of chronic diseases, including diabetes mellitus, ischemic heart disease, stroke, cancer, chronic kidney disease, non-alcoholic fatty liver disease and neurodegenerative diseases, which affect the quality of life of the elderly and influence their life span. This phenomenon is suggested to arise due to the weakening of the regulatory mechanisms of the immune response, and the persistence of exogenous and endogenous (reflecting oxidative cell injury) antigenic challenges, so it is referred to as oxi-inflamm-aging. Considering that the development of age-associated chronic inflammation is "silent", i.e., without clinical signs until the aforementioned complications become apparent, it is important to identify the biomarker(s) or pattern/cluster of biomarkers for this inflammation. It is also important to define new strategies to combat the "silent" damage induced by chronic inflammation. Given that at present there are no reliable biomarkers for chronic inflammation, this review points out the problems in defining biomarker(s) or patterns/clusters of biomarkers for chronic inflammation in order to stimulate further research and points to some possible routes of investigation.

Key words: longevity, low-grade chronic inflammation, non-communicable diseases, oxi-inflamm-aging, biomarkers of chronic inflammation

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Human longevity, genetics, and environmental factors

Even in the most developed countries, average life expectancy at birth (defined as how long, on average, a new-born can expect to live if current death rates do not change) did not exceed 40-45 years until a few centuries ago (1). However, average life expectancy at birth has substantially increased since then (1). For example, the global average life expectancy at birth had more than doubled from 1900 to 2019, so in 2019 it was above 70 years (https://ourworldindata.org/life-expectancy). However, it is noteworthy that the inequality of life expectancy is very large across and within countries (2). In 2019, the country with the lowest life expectancy was the Central African Republic with 53 years, whereas in Japan life expectancy was 30 years longer (2). In 2019, life expectancy at birth for women in Serbia was about 78.4 years, while life expectancy at birth for men was about 73.1 years on average (3). It is well-established that gains in average life expectancy at birth over last centuries can be attributed to a number of factors, including rising standards of living, improved environmental conditions (in particular clean, safe water and food), and greater access to health services, which have also been ameliorating constantly (4,5,6). Besides, genetic factors have been suggested to contribute to the increase in average life expectancy at birth (1). This notion is based on data indicating that throughout evolution infectious diseases have been a pervasive threat for survival, so strong immune responses and inflammation in early life have been crucial for the survival of humans in the unforgiving environment of our ancestor (1). Thus, it has been assumed that genes and gene variants associated with strong inflammation have been positively selected during evolution, contributing to the reduction of infant mortality and thereby to survival to reproductive age (1). Consequently, in the contemporary world, a wide range of chronic diseases associated with aging, such as diabetes mellitus, ischemic heart disease, stroke, cancer, chronic kidney disease, non-alcoholic fatty liver disease and neurodegenerative disorders, which are also called non-communicable diseases, became the major factor limiting longevity (7,8). Indeed, with aging, the incidence of these diseases substantially increases, so the majority of patients with a chronic ailment are over the age of 65 (as 80% of these older adults have one chronic condition), accounting for approximately 60% of all deaths (7,8,9). Empirical evidence that chronic inflammation plays an important role in disease onset and/or progression seems to be strongest for type 2 diabetes and cardiovascular diseases (10). However, there are also data linking low-grade chronic inflammation with the development of other non-communicable diseases (8,10). To underscore the significance of inflammation in their development, *Time* magazine labelled inflammation “The Secret Killer” on its cover in 2004 (11). Thus, as it has been already noticed by McDade (12), ironically, despite acute inflammation comprising a critical line of defence against infection and injury, without whose protection even minor injuries or infections can become potentially life-threatening, chronic inflammation may be a contributing factor to the development of serious diseases affecting human lifespan. The most compelling evidence for an association between chronic inflammation and disease risk comes from randomized controlled trials that have tested drugs or biologics that target specific pro-inflammatory

cytokines. Meta-analysis of eight randomized controlled trials encompassing a total of 260 participants revealed that anti-tumour necrosis factor-α (anti-TNF-α) therapy in patients with rheumatoid arthritis significantly reduces insulin resistance (13). Additionally, it was noticed that patients with rheumatoid arthritis treated with TNF-α inhibitor etanercept have a significantly lower risk for developing Alzheimer's disease compared with general adult population (14). In addition, a double-blind control trial encompassing more than 10,000 adults with a history of myocardial infarction and elevated circulating levels of C reactive protein (CRP) treated with canakinumab, the IL-1β inhibitor, showed that, compared with placebo, this drug at the effective dose (150 mg every 3 months), independent of lipid-level lowering, diminished the rate of recurrent cardiovascular events (15). Although the association between inflammation and a wide range of chronic diseases is widely recognized (16), the causality and the degree to which inflammation contributes to their development has not been well understood yet. Additionally, it should be pointed out that, depending on the degree and extent of the inflammatory response, metabolic and neuroendocrine changes can occur to conserve metabolic energy. Namely, in this situation more nutrients are allocated to the activated immune system, leading to the so-called energy-saving behaviours, also known as "sickness behaviours", which encompass sadness, anhedonia, fatigue, reduced libido and food intake, altered sleep and social-behavioural withdrawal (17-20). Of note, this is important as it can be critical for survival during times of physical injury and microbial threat (21).

There is evidence that the risk of developing chronic inflammatory diseases affecting adulthood health and risk of mortality arises during early development (12,22,23). Studies in humans reveal low levels of chronic inflammation in some parts of world, despite higher burdens of infectious disease, and point to nutritional and microbial exposures in infancy as important determinants of inflammation in adulthood (12). Thus, it has been suggested that early environment influences responses to inflammatory stimuli later in life, with implications for the association between inflammation and chronic diseases, by shaping the regulation of inflammation (12). However, it should be pointed out that there are also data indicating that immune system exhibits a significant level of plasticity throughout the lifespan (9,24-26). The major risk factors for developing chronic inflammation throughout the lifespan are unhealthy lifestyle, including lack of physical activity, poor diet, stress, excessive tobacco and alcohol consumption, exposure to radiation, and infection with pathogenic microorganisms (7,9,24-27). All these factors are shown not only to induce inflammation, but also to dysregulate inflammatory pathways, leading to the development of life-threatening chronic diseases (9,24-27). Additionally, based on studies in elderly people and centenarians, which revealed that several polymorphisms of important genes involved in immune responses and inflammation are present at a different frequency in long-lived people compared with young subjects, it has been suggested that genetic factors also contribute to the development of chronic inflammation with aging (28-31). In the same line are data indicating that the same gene polymorphism can have beneficial or detrimental effects at different ages, a phenomenon

referred to as “complex allele timing”, so gene variants that are apparently neutral at a young age show a different biological role at a later age in terms of phenomena such as apoptosis, cell proliferation, and cell senescence (1,32).

Low-grade chronic inflammation and human longevity

Generally, inflammation is an essential local body’s response against harmful pathogens or any type of injury, which helps to maintain tissue homeostasis and provide species survival (33,34). This response involves mainly neutrophils and macrophages and persists only for a short time, due to coordinated action of various defence components, including immune cells, endogenous anti-inflammatory agents, and tissue remodelling processes, which enable its resolution by facilitating the elimination of pathogens, infected/injured cells, and repairing of damaged tissues (35). However, if this intricate acute inflammatory response fails to resolve and persists, more defence components are mobilized, creating a long-term unresolved immune response known as chronic inflammation (35). Chronic inflammation typically involves macrophages and lymphocytes and manifests in a low-grade manner (as judged by a small rise in immune system markers in blood or tissue) at the systemic level for a prolonged period, so it is also called low-grade persistent inflammation (36). As we age, acute, beneficial transient inflammatory processes become chronic (37,38), leading to the phenomenon referred as oxi-inflam-aging (39). It has been suggested that this could happen not only due to weakening of the regulatory mechanisms of the immune response, but also due to the persistence of exogenous and endogenous antigenic challenges (40,41). In favour of the former are findings indicating the presence of mega T lymphocyte clones specific for antigens of common viruses, such as cytomegalovirus or Epstein-Barr virus in the elderly (31,40,42). On the other hand, given that mitochondrial reactive oxygen species (ROS) production is considered to be the first event in the aging process, it was assumed that mitochondrial DNA fragments generated by continued ROS leakage in the mitochondria act over time as danger or damage-associated molecular patterns (DAMPs) that can bind to pattern recognition receptors (PRR) and, through activation of the nuclear transcription factor kappa b (NF-κB), mediating induction of various pro-inflammatory genes in innate immune cells (43-45), boost inflammation (46,47). Specifically, NF-κB regulates the expression of cyclooxygenase-2 (COX)-2, inducible nitric oxide synthase (iNOS), TNF-α, and pro-inflammatory interleukins IL-1β, IL-6 and IL-8 (48,49). In the oxidative stress-induced inflammation upregulation of COX-2, iNOS, an aberrant expression of TNF-α, the most potent pro-inflammatory cytokine so far discovered, and IL-1, IL-6 and IL-8 have been found (50). IL-6 is shown to induce the activation of signal transducer and activator of transcription (STAT)3 protein, followed by its Janus-activated kinase (JAK) 1, 2, and 3 phosphorylation and nuclear translocation where it binds to the DNA and regulates transcription of genes implicated in several types of immune and inflammatory responses (51-54). What adds an extra weight to NF-κB role in deregulation of inflammatory response and development of chronic inflammation are findings indicating that NF-κB also has a role in regulating the activation of inflammasomes, innate immune

system receptors and sensors that regulate the activation of caspase-1 and induce inflammation in response to infectious microbes and molecules derived from host proteins, contributing to a host of inflammatory disorders (55,56). Altogether, deregulated NF-κB activation is suggested to be a hallmark of chronic inflammatory diseases (57). It has also been revealed that mitochondrial ROS can directly activate NACHT, LRR, and PYD domains containing protein 3 (NLRP3) inflammasome, which leads to the processing and secretion of the pro-inflammatory cytokines interleukin (IL)-1 and IL-18 thereby contributing to maintenance of inflammation (58-61). Thus, it was assumed that DAMPs-associated activation of the transcription factor NF-κB and the inflammasome pathways, resulting in the sustained production of pro-inflammatory compounds, together with oxidant compounds, leads to cell senescence and tissue damage with the release of new DAMPs, in vicious spiral feedback (27). The reshaping of the cytokine expression pattern, with a progressive tendency toward a pro-inflammatory phenotype, is believed to play a key role in the remodelling of the immune system at an older age (27). Complementarily, an inability to fine-control inflammation is suggested to be a marker of so-called "unsuccessful" aging, i.e., aging associated with chronic inflammatory diseases (27). What corroborates the latter are data indicating that anti-inflammatory side of the immune system, encompassing anti-inflammatory cytokines and families of soluble receptor antagonists, is also deregulated, and consequently ineffective in damping down the inflammatory episode in a timely and effective manner (62). Our data obtained in rats speak in favour of the previous notion (63,64). The molecular processes that damp down inflammation, including so-called specialized pro-resolving mediators (SPMs), have been underinvestigated in aging (62). Thus, the loosening of the cytokine balance between the pro-inflammatory mechanisms and anti-inflammatory control or resolving mechanisms (65,66) is shown to be a characteristic feature of both aging and aging-related diseases (62). Taking into consideration all the aforementioned findings, the aging of the immune cells could be viewed as a result of the aging process, but also as a driver of this process, through the production of oxidant and inflammatory compounds, which cause damage and induce senescence within other tissues, ultimately leading to low-grade persistent inflammation (67).

Biomarkers for low-grade chronic inflammation

Chronic inflammation is considered to be a major health care problem due to its "silent" development, with no clinical signs, until complications are evident (68). Thus, defining biomarkers for low-grade chronic inflammation seems to be an important step in fighting the silent damage induced by chronic inflammation and possibly preventing chronic inflammatory complications. However, at present, there are virtually no markers in use capable of segregating acute and chronic inflammation associated with chronic pathology. Most inflammatory serum markers, such as prostaglandin E2 (PGE2), high sensitivity C-reactive protein (hs-CRP), TNFα, IL-1β , IL-6, IL-8, and a myriad of other molecules associated with inflammation: transcription factors (NF-κB, STAT3), pro-inflammatory enzymes as COX-2, matrix metalloproteinases (MMPs), cell adhesion

molecules (CAM), vascular endothelial growth factor (VEGF), to name a few, are already up-regulated in the acute phase (9,69). Thus, they are unsuitable for detecting the development of chronic inflammation. Additionally, it has been observed that at least some of them are increased only in chronic diseases associated with specific pathologies (9,69). To monitor inflammation associated with aging in a meaningful way, the markers used must specifically reflect the low-grade chronic inflammatory process and must be predictive of future health status. In this context, the range of potential biomarker (s) or patterns/clusters of biomarkers which can be used to assess chronic inflammation in human nutrition studies in the general population (healthy population) was considered by an expert group of the International Life Sciences Institute (ILSI) Europe (70). However, although the concentration of many of these biomarkers changes with aging in some studies (71-76), there is no consensus yet as to which marker(s) or pattern/cluster of markers best represent low-grade inflammation or differentiate between acute and chronic inflammation (70,77). It is noteworthy that some of the aforementioned inflammation markers (e.g. proinflammatory cytokines, hpCRP). have been found to be associated with future risk of cardiovascular diseases (70,77). However, there are several important issues preventing their use as determinants of low-grade inflammation. They are non-specific acute-phase response and pro-inflammatory response markers, and are thereby not representative for low-grade inflammation by themselves (77). Additionally, even in healthy individuals, there is great variation in the values of these biomarkers, reflecting sex, genetics, physical (in)activity, smoking, gut microbiota composition, diet, use of medications and other factors such as emotional stress, pollution, viral infection, and sleep behaviour (77). Given that health is defined by the ability to adequately adapt to everyday stress challenge (78), it seems obvious that measuring inflammatory biomarkers` concentrations under basal conditions is less informative in respect to health risks than measuring changes in their concentration in response to a challenge. Thus, this response to various challenges, including an oral glucose load (79), an oral fat load (80), acute exercise, administration of bacterial lipopolysaccharide (81), exposure to UV irradiation (82) has been measured (77). However, the value of data obtained in these studies seems to be limited, as challenges have been poorly standardized (68).

Although at present there are no reliable markers of low-grade inflammation associated with potentially life-threatening chronic conditions, there is some realistic hope in the development of new technologies for the discovery of biomarker signatures that reflect low-grade chronic inflammation (83,84). This hope is based on an impressive growth in innovation in ‘omics’ technologies that provide wide opportunities for biological sample characterization with patterns and clusters of markers (signatures or fingerprints), and development of bioinformatics tools to interpret these complex data in the context of huge existing biological knowledge in the literature and databases, viz. the so-called network biology (85,86).

Considering all the aforementioned, it is noteworthy that some efforts have been made to identify biomarkers that sense the change in immune status generated by chronic inflammation. In this context, it is important to point out that high levels of circulating

pro-inflammatory molecules activate regulatory arms of the immune system, including myeloid derived suppressor cells (MDSCs), leading to a dysregulated immunity and weakening of the immune effector arm, and exposing the host to an array of complications (87). These complications include increased susceptibility to opportunistic infections, tissue transformation, malignancies, and other inflammatory insults (87). Thus, it has been suggested that monitoring MDSCs in terms of their number and molecular features, such as the production of NO and ROS and pro-inflammatory calcium binding S100A8/A9 proteins, PD-L1 (the ligand for the inhibitory receptor on T-cells), and CD39 and CD73 (the molecules working together in conversion of extracellular ATP into adenosine to suppress T-cells), correlating with their suppressive activity (68). Alternatively, monitoring of the cells suppressed by MDSCs has also been suggested (68). One of the most prominent effects of MDSCs in chronic inflammation is T- and NK-cell dysfunction imposed by suppressing their proliferation, cytokine production and killing ability (88-91). This dysfunction is associated with down-regulation of surface expression of CD247, the TCR ζ chain, which could be followed by flow cytometry (68). Another candidate should be CD4+CD25+ T regulatory (Treg) cells, whose functions and fitness are critical to maintain immunologic balance, including inflammation (92), as accumulating evidence suggests that their frequencies are increased in the elderly and experimental animals, and shown to play a crucial role in aging and age-related diseases (93-98). Therefore, the analysis of their frequency and functional properties could provide sensitive biomarkers of inflammatory status during aging.

However, it should be noted that, although monitoring the aforementioned immune biomarkers is suggested to be a useful tool in monitoring the development of low-grade chronic inflammation, the discovery of additional new biomarkers is necessary to validate their usefulness (68).

Conclusion

In conclusion, it is well-established that low-grade chronic inflammation associated with aging participates in the development of an array of chronic diseases that dominate present-day morbidity and mortality worldwide and limit human longevity. Thus, defining biomarkers for low-grade chronic inflammation is important not only in estimating biological age and predicting the longevity of an individual, but also as a prerequisite for formulating successful strategies to prevent/postpone the development of age-associated chronic inflammation, and thereby to assure better health for adults. Unfortunately, there are currently no highly effective laboratory measures to assess individuals for chronic inflammation, and diagnoses are only undertaken when patients develop a clinically manifest medical condition which is associated with inflammation. However, a huge growth in innovation in ‘omics’ technologies, in conjunction with the development of bioinformatics tools, provides realistic hope for defining biomarkers or patterns/clusters of biomarkers for age-associated chronic inflammation. In the same vein, there have been complementary investigations of the effects of chronic inflammation on the changes in distinct types of immune cells from blood, and accordingly an immune

system biomarker algorithm for the evaluation of the immune status with high sensitivity and accuracy, and consequently for predicting an inflammatory state.

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Biomarkeri hronične inflamacije povezane sa starenjem kao prediktora dužine života

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Kratak sadržaj

Činjenično je dobro argumentovano da hronična inflamacija niskog stepena koja se javlja u toku starenja ima važnu ulogu u razvoju čitavog spektra hroničnih bolesti, uključujući šećernu bolest, ishemijsku bolest srca, moždani udar, malignu bolest, hronično oštećenje bubrega, nealkoholnu masnu bolest jetre, neurodegenerativne i autoimunske bolesti, koje utiču na kvalitet i dužinu života starih osoba. Smatra se da ovaj fenomen nastaje kao rezultat slabljenja regulatornih mehanizama imunskog sistema i perzistentnog izlaganja organizma delovanju egzogenih i endogenih (generisanih oštećenjem ćelija oksidativnim stresom) antigenskih izazova, što se u literaturi opisuje terminom oksidativno-inflamatorno starenje. Imajući u vidu da se hronična inflamacija razvija klinički „nemo“, odnosno da postaje manifestna tek kada se razviju prethodno pomenute komplikacije, jasno je koliko je važno identifikovati biomarker(e) ili obrasce/klastere biomarkera te inflamacije. S obzirom na to da u ovom trenutku nema pouzdanih markera hronične inflamacije, ovaj pregledni rad je tako koncipiran da ukaže na probleme u identifikaciji biomarkera ili obrazaca/klastera biomarkera hronične inflamacije, s ciljem da stimuliše dalja istraživanja, ali i da da smernice za buduća istraživanja.

Ključne reči: životni vek, hronična inflamacija niskog stepena, nezarazne bolesti, oksidativno-inflamatorno starenje, biomarkeri hronične inflamacije