

# IMMUNOSENESCENCE, INFLAMMAGING AND RESILIENCE: AN EVOLUTIONARY PERSPECTIVE OF ADAPTATION IN THE LIGHT OF COVID-19 PANDEMIC

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## SUMMARY

The evolution of immunology enabled the study of role of innate and adaptive immunity in systems biology network of immunosenescence and inflammaging. Due to global reduction in birth rates and reduced mortality, in year 2025 there will be about 1.2 billion of people over age of sixty, worldwide. The notion that the real age is not chronological, but the biological one led to the concept of "bioage", defining the biologic reactivity and resilience, including the immune competence of an individual. A competent immune network, systemic and mucosal is intrinsic to resilience and homeostasis of the human holobiont as the unit of evolution. In elderly, the immunosenescence could be associated with higher levels of proinflammatory mediators (such as IL-6), frailty and mortality. Pro-inflammatory state in elderly is denoted as inflammaging, characterized with low-grade (sterile) inflammation, as a physiologic response to life-long antigenic stimuli. When under control, inflammaging could be regarded as an efficient defense mechanism, opposed and regulated by anti-inflammatory pathways and molecules. Immunosenescence. The emerging concepts of "individual immunobiography" and "trained immunity" speak in favour that the immunological experience during the life would shape the ability of each individual to respond to various stimuli, strongly influencing the elements of innate and adaptive immunity, including macrophages and innate lymphoid cells. Older age is one of the main risk factors for the severe clinical picture and adverse outcome of COVID-19 infection, due to immunosenescence and chronic low-grade inflammation (inflammaging), both characterizing the immune reaction in elderly. The senescent immune system, along with the advanced process of inflammaging is prone to react with uncontrolled activation of innate immune response that leads to cytokine release syndrome, tissue damage and adverse outcome of infection. Further research is aimed to nutritional and pharmacologic (immunomodulatory) interventions to influence the process of bioaging and immunosenescence, and to modulate the reaction of elderly to infection, including the COVID-19.

**Key words:** COVID-19

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## INTRODUCTION

During past 100 years, the biomedical science has witnessed the discoveries that represented the foundation of immunology as a scientific discipline and its development to understand the immune response genes within MHC, idiotypic networks and the mechanisms of T lymphocytes instruction. The path from description of phagocytosis by Metchnikoff and production of specific antibodies by Ehrlich to description of lymphocyte recirculation by Gowans and pattern recognition receptors by Janeway, together with discoveries in biotechnology and production of monoclonal antibodies has paved the way to integrative systems biology in elucidating the mechanisms of human homeostasis, resilience and disease development (Kaufmann 2019).

Recently published perspective of immunity by equilibrium speaks of four types of response that are mutually inhibitory over time and depending on type of antigenic stimulus. According to perspective, these types of response would be defined by major types of cells involved, Tregs of different phenotype being important component of regulation (Eberl 2016). Health

would be characterized by equilibrium of 4 types of response, and the opposite, the absence of one type of response would lead to augmentation of other type of responses, potentially leading to inflammatory pathologies. In light of this, the immunology should be situated in the wider context of physiology and ecology, representing the central component of a network of partner physiological systems to maintain homeostasis (Eberl 2018). Thus, the evolution of immunology also enabled the study of role of innate and adaptive immunity in systems biology network of immunosenescence and inflammaging.

## OLD AGE: SENESCENCE, IMMUNOSENESCENCE AND INFLAMMAGING

„All diseases run into one, old age“  
Ralph Emerson

Due to global reduction in birth rates and reduced mortality, in year 2025 there will be about 1.2 billion of people over age of sixty, worldwide. According to demographic projections, this number will be approaching two

billion, by the year 2050. However, it is important to be aware that the increase in lifespan does not coincide with healthspan. The notion that the real age is not chronological, but the biological one led to the concept of „bioage“, defining the biologic reactivity and resilience, including the immune competence of an individual (Crossley 2019). This concept led to a great interest in elucidating and targeting biological processes that are associated with aging, such as the age-related decline of the immune response to infections and vaccination. The basic and translational research, based on systems biology are striving to answer the question what would be the biological threshold for senescence/immunosenescence and could it be a reverse process.

Senescence, as a key-hallmark of aging is characterized by cells that stop dividing and enter a state of permanent growth arrest. Senescent cells in various tissues and organs are intrinsic to aging process, but their presence is associated with chronic diseases, as well. The senescent cells are usually found in tissues of older individuals of higher biological age, cancer patients undergoing chemotherapy and sites of pathology of age-related diseases. The results of previously mentioned meta-analysis that included 51 study and over two thousand participants (Crossley 2019) showed that there is an overall positive correlation between senescence and chronological age. However, the authors also noted variable degree of senescence and its association to chronological age, across various tissues observed. The authors speculate, this could be due to variable natural cell turnover in different tissues, but also due to tissue-specific response to environmental exposures that evoke different mechanisms of tissue and organ response to cytotoxic stress, as well. In addition, it could be also the question of different clearance capability for senescent cells across different tissues. Thus, the various degree of senescence in different tissues and organs is closely linked to resilience of the organism, as a whole.

A competent immune network, systemic and mucosal is intrinsic to resilience and homeostasis of the human holobiont as the unit of evolution. Immunosenescence is characterized with declining function of the immune system that leads to higher incidence of infection, cancer and autoimmune related mortalities, and poorer response to vaccination, as well. In elderly, immunosenescence could be associated with higher levels of proinflammatory mediators (such as IL-6), frailty and mortality. Pro-inflammatory state in elderly is denoted as inflammaging, characterized with low-grade (sterile) inflammation, as a physiologic response to life-long antigenic stimuli. When under control, inflammaging could be regarded as an efficient defense mechanism, opposed and regulated by anti-inflammatory pathways and molecules. Immunosenescence and inflammaging should be regarded as separate, but highly intertwined entities (Pawelec 2018).

## **MECHANISMS OF AGING: CHANGES IN INNATE AND ADAPTIVE IMMUNE SYSTEM**

Dysregulation of immune system, associated with aging is characterized with reduced effectiveness of antibody and cellular responses. This general reduction of immunologic capability is multifactorial and it is influenced with host (genetics) and extrinsic/environmental factors, such as nutrition, obesity, physical exercise, smoking, comorbidities and comedication, physical and mental stress and previous exposure to microorganisms and toxins. It is important to point out that the lower immunologic responsiveness is not exclusively linked to chronological age and it has been shown that some younger individuals can also exhibit the pattern of hyporesponsiveness. On the contrary, some older individuals can exhibit relatively good response (Lee 2016).

The emerging concept of „individual immunobiography“ speaks in favour that the immunological experience during the life would shape the ability of each individual to respond to various stimuli, strongly influencing the elements of innate and adaptive immunity, including macrophages and innate lymphoid cells (Del Giudice 2018). These changes of age-associated impairment in immune cell function start with impairment of metabolic regulation. The quiescent cells use oxidative phosphorylation (OX-PHOS) aerobic energy pathway which produces 36 ATPs per metabolized glucose. The activated cells use anaerobic glycolysis (Warburg effect) for quick demands which produces only 2 ATPs per metabolized glucose. T cells in elderly use different metabolic pathways that are intrinsic to non-senescent and/or normally activated immune cells (mTOR/AMPK/ERK/DUSP4 and 6), but in an altered manner. This altered manner of using the metabolic pathways is also reflected in changes in composition and organization of cell membrane and membrane signaling molecules. Upon the stimulation with the same or different type of antigen, due to epigenetic changes in modulation of cell metabolism, immune cells of elderly are not capable of eliciting faster and higher response, preferably using the slower path of OX-PHOS (Bekkering 2016).

The age-related changes in innate immunity are closely linked to concept of „trained innate immunity“ and hormesis. In definition, hormesis means process in a cell or organism that exhibits a biphasic response to exposure to increasing amounts of a substance or condition. Cellular and humoral elements of innate immunity represent a first line of defence to pathogens. In addition to localization and timing, the nature and extent of innate immune response also depends on dose of pathogens. This, slow-acting, adaptive mechanism of innate immune response (not to be confused with classical involvement of B- and T-lymphocytes in the mechanisms of adaptive/acquired immunity) reflects the

mechanism of hormesis. This adaptation of innate immunity allows modulation of response to certain specific challenge and may prevent overreaction to danger signals (Schmidt 2014).

The term „trained innate immunity“ coined and introduced by Franceschi and coworkers, in 2000, is associated with inflammaging which denotes chronic, sterile inflammation. Trained immunity represents an innate immune memory program, induced by repetitive infections and/or vaccinations that results in more active functional state of innate immune cells. Thus, immunological memory encompasses both innate and adaptive immune memory and trained innate immunity (TII) denotes enhanced innate immune state that is, at least in part responsible for low-grade inflammation in elderly (Netea 2017).

### **IMMUNOSENESCENCE AND INFLAMMAGING: AN EVOLUTIONARY PERSPECTIVE OF ADAPTATION?**

The process of aging could be regarded as a cumulative result of dysregulation of different body systems as a decline from normal (homeostatic) regulatory level to an altered state of dyshomeostasis. The state of dyshomeostasis should not be regarded as a state of disease, but as a reflection of adaptation to intrinsic and extrinsic stimuli during aging. So, the bioaging is associated with immunosenescence and inflammaging that put the human organism to the continuum of an altered state of bioreactivity, across the age spectrum of each individual. From a pathophysiological standpoint, this continuum of altered states of bioreactivity, caused by „canalized“ dysregulation could be regarded as an optimization of response to imperfect situation.

### **SHOULD WE INTERVENE AND HOW: REJUVENATION AND VACCINATION?**

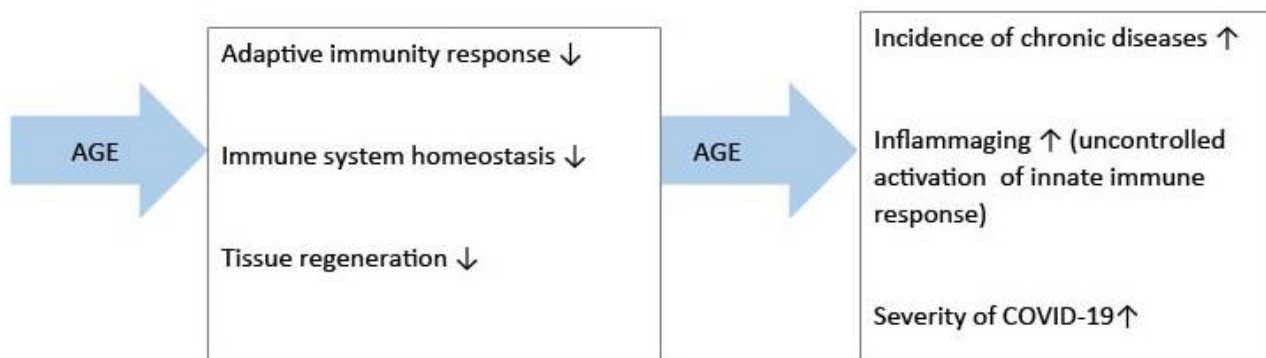
The spectrum of aging, including immunosenescence is a plastic process that could be influenced with nutritional and pharmacologic (immunomodulatory) interventions. It seems that there is a close connection between the intake of bioactive nutrients, immune functions and inflammation, pointing to possibility of modulation of the process and the rate of immunosenescence. It has been shown that Mediterranean diet, rich in fruits, vegetables, whole grain, legumes and olive oil, along with reduced consumption of red meat is capable of attenuation of inflammation and oxidative stress and maintenance of gut microbial eubiosis. Micronutrients such as vitamins and minerals are essential for the efficient performance of the immune system. Probiotics, prebiotics, symbiotics, nutraceuticals, such as carotenoids, dietary polyphenols and dietary lipids (PUFAs: eicosapentanoic and docosahexaenoic acid) has been

shown to modulate immune response. Clinical approaches that have been in research include growth factors, such as thymopoietic IL-7 and checkpoint inhibitors, such as PD-1 and CTLA-4, that promote immunological control of cancer cells by blocking the immune inhibitory responses that are evolutionary designed to prevent continuing immunological response once an antigenic stimulus has been eradicated (Elias 2018). The MAPK signaling pathways represent complex systems with three main subgroups: Erk, Jnk and p38 that regulate the functions of innate and acquired immunity. The blocking of p38 MAPK signaling pathway can improve the activity of effector memory CD8+ cells, and combined blocking of p38 and a family of stress sensor proteins (sestrins that promote pro-aging activities in T senescent lymphocytes) restored the activity of T cells, derived from older humans (Lanna 2017). A number of recent publications speak in favour of blocking the mTOR pathway in order to ameliorate the immune response and improve the hematopoietic cell function, by using rapamycin and everolimus (Mannick 2014).

A very interesting approach to raise protective immunity in elderly is the development of novel vaccines, containing various adjuvants, aimed to trigger multiple TLRs in order to overcome the age related defects in CD4 T cells response (Tye 2015). Another, very intriguing approach is in diminishing the HCMV (human cytomegalovirus)-associated immunosenescence by vaccine and antiviral agents (letermovir) that inhibit HCMV replication (Marty 2017).

### **IMMUNOSENESCENCE AND TRAINED IMMUNITY: IMMUNOLOGIC RESPONSE AND COVID-19**

According to viewpoint of different research groups, the dichotomy between the innate and the adaptive immunity represents the simplification, and is not strictly distinct during the immunologic reaction, due to the fact that many cells of the immune system play the roles in both arms, innate and adaptive immunity. The number of experiments provided the proof of concept that innate immune mechanisms can adapt and induce the non-specific immunological memory upon exposure to different, non-related antigens, due to repetitive infections and/or vaccinations, during the lifetime of an individual. Evolutionary, the trained immunity represents very old and highly conserved mechanism, that evolved for protection of multicellular organisms, lacking the adaptive immune response. The ongoing research of this concept of „trained immunity“ has shown that the cells of monocytic lineage (monocytes and macrophages) and certain ILCs (NK cells) are the cells in which resides the innate immune memory. In addition, further research provided the close link between immune signaling, cellular metabolism and epigenetic reprogramming (Netea 2017).



**Figure 1.** The remodeling of immune response: Immunosenescence, inflammaging and COVID-19

In conjunction with symptoms of severe cases of COVID-19 at clinical level, the molecular alterations reveal the state of hyperinflammation, in most severe cases the systemic inflammatory response, known as cytokine release syndrome (cytokine storm), due to massive production and release of IL-1, TNF-alpha and IL-6, the most important cytokines of innate immune response. Thus, the cytokine storm results from sudden increase in circulating levels of different pro-inflammatory cytokines, resulting in increased influx of immune and inflammatory cells (macrophages, neutrophils, lymphocytes) into the site of infection. The outcome of this process is tissue destruction, multi-organ failure, and ultimately death. Older age is one of the main risk factors for the severe clinical picture and adverse outcome of COVID-19 infection, due to immunosenescence and chronic low-grade inflammation (inflammaging), both characterizing the immune reaction in elderly (Domingues 2020).

The immune system in elderly is characterized with remodeling of immune response, being less capable of mounting the adequate specific response to neo-antigens. The hallmark of this immune remodeling is lower count of naive T cells, expansion of memory T cells with a shrinkage of T cell diversity repertoire, and impaired function of antibody-secreting cells. The senescent immune system, along with the advanced process of inflammaging is prone to react with uncontrolled activation of innate immune response that leads to cytokine release syndrome, tissue damage and adverse outcome of infection (Cunha 2020) (Figure 1).

## CONCLUSION AND A VIEW TO FUTURE

The remodeling of immune response in immunosenescence and inflammaging predisposes the elderly to adverse outcome of infection, including COVID-19. Already, there exist several approaches to influence the process of immunosenescence and inflammaging, including nutritional and pharmacologic (immunomodulatory) interventions. In addition, the study of immune response to COVID-19 infection in elderly pointed to biomarkers of the remodeled immune response as to

new potential targets in these patients., aimed to elicit a functional adaptive immune response and to diminish the harmful pro-inflammatory state of disease. The ongoing research of therapeutic approaches to COVID-19 is focused to antiviral drugs, specific immunoglobulins and immunomodulatory agents, including biologics targeting different cytokines.

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### Contribution of individual authors:

All authors reviewed and discussed the manuscript draft and contributed to the final manuscript and all authors give final approval of the version to be submitted.

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