HOLISTIC APPROACH TO AGE-RELATED RESTRUCTURING OF THE IMMUNE SYSTEM (QUEST FOR INTEGRATIVE MEDICINE)

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Ancient evolutionary involution of thymus in vertebrates is the only physiologic process that shows marked changes in the aging body. Due to thymic involution, immunosenescence is characterized by progressive dysfunction of the adaptive type of immunity mediated by lymphocytes, accompanied by increased activity of the innate type of immunity mediated primarily by macrophages. In the elderly, development of age associated diseases represent a dynamic evolutive stochastic non-linear process resulting in various physiologic states, which at the same time are predictors of increased multimorbidity and grave infections. Transition from dynamic homeostasis to chaotic behavior can be provoked by bias in cellular interactions and long lasting imbalanced secretion of proinflammatory or anti-inflammatory chemokines. Whether or not some of the aberrant intra- and or intercellular homeostatic mechanisms in the immune system could propagate pathogenetic events in various clinical manifestations can only be expressed by probability, which depends on the genetic, evolutionary, environmental, epigenetic, and lifestyle factors.

Key words: thymus involution, immunosenescence, immune system remodeling, macrophages, innate immunity upregulation

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PROLOGUE

Nothing in biology makes sense except in the light of evolution (Theodosius Dobhzansky, 1973)

Genetic and behavioral variabilities (biodiversity of algorithms) of *Homo sapiens* based on Ch. Darwin and A. R. Wallace co-developers of the theory of evolution, are functionally regulated, coordinated and balanced by complex interactions at the intracellular level (among molecules), intercellular level (among cells), organ level (among organs), integrated at the level of the whole body (biological individuality), and in addition deeply influenced at the environmental level (various social and cultural elements), created by natural evolution over millions of years.

INDIVIDUALITY OF THE IMMUNE SYSTEM

The immune system is creation of evolution. It has arisen by exploitation of error nucleotide replication and it is more infallible than any other aspect of biological functions. (Macfarlane Burnet, 1972)

The brain and the immune system establish individuality at two levels: they help us adapt to life and so preserve us, and they make a record of what has happened. (Irud Cohen, 2000)

There are three ways in which information about past is archived in such a way that it can be used to improve future chances of survival. These are the immune system, the nervous system, and culture. (Richard Dawkins, 2013)

The immune system is one of the most important integrative multicellular systems in the body, which by continuous communications, interactions and balanced coordination with neural, endocrine and metabolic systems records, protects, creates and defines our individuality. The immune system as a sensory organ actively participates in maintaining body homeostasis by protection 1) against external hazards (infections by bacteria, viruses, parasites, and allergens), 2) against internal hazards (anti-self-reactivity and surveillance against tumors), and 3) by active participation in the pathogenesis of practically all diseases.

EVOLUTION OF THE IMMUNE SYSTEM

...no biological problem is solved until both the proximate and evolutionary causation has been elucidated... (Ernst Mayr, 1982)

From the evolutionary aspect, there are two types of immunity, innate and adaptive immunity.

Innate type of immunity
It is the phylogenetically oldest conserved protection mechanism against pathogens in animal kingdom, mediated by macrophages. Macrophages are strategically distributed in all tissues and organs, where they signal immediate potent nonspecific process of phagocytosis *via* TOL-like receptors, ingest and eliminate microbes, dead cells and/or their debris, and by additional activation modulate their dynamic relationship mutually interacting in secretion of pro-inflammatory and/or anti-inflammatory (protective) set of chemokines.

A***daptive type of immunity***
It is a phylogenetically younger, thymus dependent protective mechanism, with basic structure of Th-1 and Th-2 lymphocyte populations secreting pro-inflammatory and/or anti-inflammatory cytokines, which display extremely diverse repertoire of antigen-specific recognition receptors for identification and elimination of pathogens.

Thymus involution
Biohistorically, progressive thymic involution is the only physiologic process that shows marked changes in the aging body, representing an ancient and conserved evolutionary process in all vertebrates.

Immunosenescence
Due to thymic structural and functional involution, developing immunosenescence represents a complex process of recapitulation of inversely evolutionary pattern of the immune system.

Remodeling of the immune system is defined by two basic coexisting cellular processes, i.e. progressive functional dysfunctions of the younger adaptive type of immunity and domination of the innate type of immunity mediated by macrophages. In aged individuals, the process of thymic involution leads to modification and modulation of the immune system making the system more adapted to cope with pathogens in local environment. From the evolutionary perspective, structural and functional changes of the immune system in aged individuals represent optimization of resources of the aging body.

INTEGRITY OF THE IMMUNE SYSTEM

The harmonious cooperation of all beings arose not from the orders of a superior authority external to them but from them, a fact that they were all parts in hierarchy of whole formatting a cosmic pattern and what they obeyed were internal dictates of their own natures. (Chuang Tze, 3rd century BC)

The immune system consists of a huge number of individual immunocompetent cells penetrating most tissues/organs in the body, which continuously receive and transmit a great variety of excitatory and/or inhibitory signals creating a dynamic network responsible for control of basic reactivity and enhancement of effectiveness of the system in performing complex physiologic functions *via* permanent activities mediated by various humoral and cellular mechanisms.

Therefore, long lasting duration of imbalanced secretion of a number of proinflammatory and/or anti-inflammatory cytokines/chemokines with their pleiotropy, redundancy, synergistic and/or antagonistic activities and parallelism can act together with bias of cellular interactions. Human beings are maintained in dynamic stationary state as a thermodynamically open system with self-organization, complexity and emergence of new order characterized by a high level of adaptation. The complex behavior of the immune system emerges spontaneously from their structure with new properties that are not simple sum of individual units. The greater basic complexity, together with better adaptability to daily perturbations, is responsible for the remarkable stability of the system.

REACTIVITY OF THE IMMUNE SYSTEM

Everything in immune phenomena is soft-edged. There is not clear absolute whether or not a given reaction occurs when cell meets antigen can be only expressed as a probability whose magnitude depends on factors... as complex at cellular level as genetic and ecological factors which determine the course of evolution on macro level. (Sir Macfarlane Burnet, 1972)

Induced by an antigen (external or internal), the immune reaction represents a series of strictly locally and timely controlled cellular events in immunocompetent cells (APC, T and B lymphocytes) located in various tissues/organs, accompanied by balanced secretion of a number cytokines expressing various functional activities. Cytokines create the most important dynamic homeostatic network of the immune system, which is composed of a number of small glycoprotein molecules secreted by two different T-lymphocyte populations that interact in a non-linear fashion.

Two basic coexisting homeostatic mechanisms are responsible for dynamic homeostasis of the immune system, i.e. linear temporal oscillation mechanism regulated by negative feedback loop (dose response) and non-linear temporal mechanism responsible for dynamic modulations (positive feedback loop) when small changes in initial conditions (various types of physical and/or psychologic stresses) can provoke exponential non-anticipated abrupt effects in the full range of the system reaction (chaotic behavior, hypercytokinemia, cytokine storm) as one of the most important features of the cytokine network.

Coexistence of two homeostatic mechanisms and their bidirectional communications with fine tuning in secretion of various cytokine profiles represent one of the most important mechanisms that, in turn, orchestrate many vital functions responsible for longevity.

AGE-ASSOCIATED DISRUPTION OF THE IMMUNE SYSTEM HOMEOSTASIS

Indeed, regulation in the organism is a central problem of physiology. (Walter Cannon, 1929)

Multiple dysfunctions of the immune system (chaotic behavior*)* could be clinically manifested by general inflammatory reaction accompanied by multiple organ dysfunctions (systemic explosion) or compensatory anti-inflammatory reaction syndrome with severe immunosuppression (systemic inplosion). Pleiotropy, redundancy, synergistic and/or antagonistic activities and parallelism can act together with bias of cellular interactions. Human beings are maintained in a dynamic stationary state as thermodynamically open system with self-organization, complexity and emergence of new order characterized by high level of adaptation.

At the clinical level, it is deeply influenced by initiation, course, gravity, and outcome of a variety of clinical manifestations primarily by increased susceptibility to infections. Taking together, trivial degrees of built-in changes, by activation of non-linear type of control mechanism can significantly contribute to clinically good or poor prognosis.

Age related decline of adaptive type of immunity

Due to physiologic thymic involution, immunosenescence is functionally characterized by quantitative reduction of naive T-cell compartment, impaired immune response to newly pathogens and vaccination, exhaustion of some T-cell clones, and reduction of T-cell receptor diversity. Thus, various age-dependent subtle genetic defects could be responsible for irregular functional maturation of common lymphoid progenitors into T-cells as central effector and regulatory cells in the immune system. Consequently, by continuous exposure to various new antigens as a result of repeated clinical and subclinical infections, memory and differentiated effector T-lymphocytes with exhausted mitotic activity, continuously selectively accumulate in the immune space/tissues.

Age related chronic low-grade inflammatory syndrome (inflamm-aging)

Aging is associated with chronic low grade inflammation called inflamm-aging. (Claudio (Franceschi, 2000)

It is tempting to suggest that inflamm-aging might be considered to be the essence of life. (Tamas Fulop, 2018)

Highly heterogeneous monocytes/macrophages with great genetic potential and ability to rapidly change their biologic activities in response to local microenvironmental signals by their power of initiation and resolution of the immune reaction play a dominant role in development and propagation of chronic inflammation in aging population. The major cause of age-associated chronic inflammation is the ability of three distinct pattern types of microbe antigen receptors (PRRs) on macrophage surface to recognize and accumulate misplaced and misfolded self-molecules from damaged cells and cell debris (wearing out process). The process of recognition elicits low grade of subclinical inflammation *via* intra-cellular pathways by excess secretion of proinflammatory cytokines IL-6, IL-1, IL-8, TNF alpha, INF alpha and beta, together with upregulation of clotting factors and CRP, along with the prevalence of myeloid over lymphoid lineages (phagocytosis) in peripheral blood and loss of self-tolerance with production of autoantibodies. Multifunctional monocyte/macrophage lineage cells, found in nearly all tissues in the body, can be additionally gradually polarized into one of two functionally distinctive subsets, i.e. M-1 subset with increased production of proinflammatory chemokines and/or M-2 subset with increased production of chemokines which promote resolution of chronic inflammation (tissue repair).

Depending on initial conditions, variable relationship between M-1 and M-2 macrophage subsets in combination with imbalance in their dynamic mutual bidirectional communications, the M-1/M-2 system can be either dynamically stable showing oscillatory character (clinical remissions) or dynamically unstable showing progressive aggravation and/or relapses of various autoimmune and inflammatory diseases.

PUBLIC HEALTH SIGNIFICANCE

The deleterious impact of age on functional integrity of the immune system was not discovered until the average of human life expectancy was approximately in the range of 40 years. However, paradoxically, over the last 150 years, in spite of decreased body complexity and declining functions of the immune system, in the second part of longevity, human life expectancy resulted in dramatic increase to the unexpected average of above 80 years.

Age-associated diseases

The state of health or disease are expressions of the success or failure experienced by the organism in its efforts to response adaptively to environmental challenges. (René Dubos, 1965)

Development of age-associated diseases is a dynamic evolutive stochastic non-linear process which can in elderly patients result in various physiologic states and diversification of their clinical phenotypes. These various physiologic states are at the same time predictors of increased morbidity, physical disability, and mortality risk rate, which is frequently clinically accompanied by multimorbidity and grave infections. In elderly patients, transition from dynamic homeostasis into chaotic behavior can be provoked by bias of cellular interactions, imbalanced secretion of different proinflammatory and/or anti-inflammatory cytokines/chemokines caused by reduced body complexity clinically manifested as premature aging, chronic recurrent infections, immunodeficiency, autoimmunity, and cancer. As a consequence, age-associated low-grade chronic inflammation represents unsolved, uncontrolled and prolonged complex cellular events with detrimental effects on health by exacerbating biologic aging and development of different age related diseases.

Thus, inflamm-aging significantly contributes to worse course of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, atherosclerosis, dementia with cognitive decline, and metabolic disorders such as visceral obesity, fatty liver, diabetes type 2, and insulin resistance.

However, whether or not aberrant intracellular or intercellular homeostatic mechanisms alone or in combination with other homeostatic interactive communications among different macrophage subsets could propagate pathogenic event(s) in direction of any of clinical entities can be expressed only as a probability depending on different mutually interrelating conditions such as **evolutionary factors** *via* variable dynamics in progression rate of physiologic involution of thymus as an ancient conserved evolutionary process in all vertebrates taking place in the second part of longevity; **genetic factors** *via* polymorphism in regulatory genes (genetic coding variants) or structural changes in affected genes by built-in restrictions of genetic programs controlling and regulating different cellular processes.

Possible consequences of these genetic events could be manifested both at the intracellular level (restrictions of various degrees of different functional programs) and intercellular level (aberrant cell dialog which might result in profound dysfunctions of various homeostatic mechanisms), such as **environmental factors** *via* disproportion between persistent antigen load and/or duration of antigenic stimulation and the capacity of homeostatic immunoregulatory mechanisms; **immune factors** *via* developing age dependent immunodeficiency in elderly population related to gradually evolving selective restriction of various genetically controlled mechanisms in the thymus microenvironment; **neuro(psycho)-endocrine-immune factors** *via* unpredictable acute grave stress and/or repeated chronic stress could also be essential for disruption of dynamic homeostasis of the immune system and transition to chaotic behavior; and finally **epigenetic factors** *via* standing at the interface of the assumed disease risk gene and environmental exposure with profound effects on developmental cell plasticity, by activating specific hypothetical disease phenotype, particularly in case of developing and aging cells.

Namely, the epigenome is a molecular code superimposed upon genome that controls how genes are turned on and off without altering the underlying DNA sequence, which in turn, may change due to an adverse environment(s) into various active disease phenotypes. All the mentioned factors can additionally contribute to genomic instability, especially in the second part of lifespan, by decreased repair capacity and cumulative damage to DNA molecules, by modification of subcellular structures that may alter gene expression patterns, by oxidative damage to vital macromolecules, and by telomere shortening in replicative cells responsible for functional decline in different tissues and organs.

INSTEAD OF CONCLUSION

Aging is a journey along the road of stochastic evolutive aging creating immunodeficiency syndrome process resembling the ***SCILLA and HARIBDA MYTH,*** when escaping one trap, one can drop in another.

POST SCRIPTUM

In contrast to genetic changes, the reversible nature of epigenetic mechanisms makes these pathways promising venues in the development of regimens against age related decline and disease (epigenetic environmental factors beneficially influencing functional activities of the immune system in aging populations) such as **public health factors** by advances in medical sciences, improved nutrition, massive vaccination, rational use of antibiotics, environmental justice and equity, improved socio-economic conditions and health care accessibility, **lifestyle factors** by modified various and specific social, historical and cultural influences in combination with compassionate health care, mindfulness, physical activity, and finally by introducing **holistic approach** in the treatment of patients including whole person body, mind and spirit (personalized medicine).

EPICRISIS

General practitioner must be primarily social worker and teacher. *(Andrija* Štampar*, creator of social medicine in Croatia, 1925)*

Historical experience together with epidemiological, clinical and laboratory studies collected in the last 150 years has already reflected in the visionary definition of health accepted by Constitution of the World Health Organization and Economic and Social Council of the United Nations, New York in 1946, by declaring that ***HEALTH IS A STATE OF COMPLETE PHYSICAL, MENTAL AND SOCIAL WELL-BEING AND NOT MERELY THE ABSENCE OF DISEASE OR INFIRMITY.***

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SAŽETAK

HOLISTIČKI PRISTUP PROCESU RESTRUKTURIRANJA IMUNOSNOG SUSTAVA U STARIJOJ DOBI (POTREBA ZA INTEGRATIVNOM MEDICINOM)

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Involucija timusa je evolucijski vrlo star i jedinstven fiziološki proces u svih kralježnjaka. Proces je intimno povezan s remodeliranjem imunosnog sustava u kojem dolazi do selektivnog slabljenja sustava adaptivne imunosti posredovane limfocitima te dominacije evolucijski starijeg sustava urođene imunosti posredovane primarno makrofazima. U starijoj populaciji dolazi do disbalansa dinamičke homeostaze zbog nedostatne komunikacije između stanica imunosnog sustava i neuravnoteženog lučenja proupalnih i protuupalnih citokina kemokina. Hoće li neke od produženih i neuravnoteženih interakcija imunosno kompetentnih stanica imati određene kliničke manifestacije u velikoj mjeri ovisi o genetskim, evolucijskim, okolišnim, epigenetskim i kulturološkim čimbenicima.

Ključne riječi: **involucija timusa, remodeliranje imunosnog sustava, urođena imunost, makrofazi, imunosenescencija**