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AGING AND IMMUNE SYSTEM: AN OVERVIEW

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Abstract: *The world is seeing a quick segment move towards a more established populace, a pattern with significant clinical, social, monetary and political ramifications. Maturing is a multifaceted procedure, including various sub-atomic and cell components with regards to various organ frameworks. An urgent part of maturing is a lot of useful and auxiliary adjustments in the invulnerable framework that can show as a diminished capacity to battle contamination, lessened reaction to inoculation, increased incidence of cancer, higher prevalence of autoimmunity and constitutive low- grade inflammation, among others. In addition to cell-intrinsic changes in both innate and adaptive immune cells, alteration in the stromal microenvironment in primary and secondary lymphoid organs plays an important role in age-associated immune dysfunction. This review will provide a broad overview of these phenomena and point out some of their clinical and therapeutic implications. This review study setting, discussing the gradual aging immune system. Data for this study is collected from different search engines like PubMed, Google Scholar, MeSH, Semantic scholar, Cochrane, NCBI, Medline, core science. A total of 53 articles were selected. The aging of the immune system is associated with dramatic changes in the distribution and competence of immune cells. Anti-Aging therapy should aim at prolonging T cells' survival while weakening inflammation prone to innate immunity.*

Key words: *immune aging; t cells; DNA damage; immunosenescence; endocrine disorder; inflammation.*

1. INTRODUCTION:

Aging is one of the most intricate and complex biological phenomena[1] . A comprehensive understanding requires an integrated approach to all physiological systems. This has captured human imagination from immemorial centuries and the search for a Fountain of Youth is still ongoing [2]. The concept of immunosenescence reflects age-related change in immune response, both cellular and serological, affecting the process of generating specific responses to foreign and self - antigen [2,3]. The decline of the immune system with age is reflected in the increased susceptibility to infectious disease, poorer response to vaccination, increased prevalence of cancer, autoimmune and other chronic diseases [4]. The metabolic changes of the aging body, including the increased presence of apoptotic cells and of oxidative stress, even in healthy conditions, induce the immune system to change its "quiescent" state to a different, often higher level of basal activation [5]. Consequently, the immune reactivity of healthy elderly people is qualitatively and quantitatively different from that of

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healthy adults [5,6]. Thus, different "normal" thresholds should be considered in the healthy aging population. By identifying the features of the normal response by the aging immune system, it would then be possible to better identify pathological responses[7] .

Progress in understanding the cellular and molecular basis of immune senescence and immune responsiveness in the elderly will allow us to develop a better targeted and effective immunization strategy[4,7]. Combating immunological aging, differences in immune responses in aged individuals often lead to a state of immunological frailty or immunosenescence[8]. Immunological frailty can be addressed through diverse strategies, including preventing infectious diseases (vaccination), ensuring adequate nutrition and physical exercise, and maintaining a high level of intellectual challenge [9]. However, implementation of such measures is a problem of resources and of public health strategies, in particular in less developed countries.

In reference to vaccination in the elderly, there is evidence that vaccination in the elderly delays the transition from the so-called "young-old" to "old-old." However, it remains difficult to identify which age groups within the elderly population should be particularly targeted by vaccination [10]. Reliable and robust biomarkers of vaccine-induced protection in the elderly (correlates of protective immunity) are needed [11]. In addition, the immune reactivity of the elderly to vaccination should be improved without triggering potentially adverse inflammatory reactions [12]. By integrating the progress made in understanding the molecular basis of immune senescence with vaccinology and gerontology, current scientific knowledge could be translated into the development of vaccination strategies for the poorest countries [12,13]. In this review, there will be an explanation of recent advances in the domain of changes in the immune system with aging and outline our vision on changes that can be dynamically reconsidered from immunosenescence to immunoadaptation.

2. MATERIALS AND METHODs:

This is a review study setting, discussing the gracefully aging immune system. Data for the study were collected from search engines like PubMed, Google Scholar, MeSH, Semantic scholar, Cochrane, NCBI. A total of 53 articles were selected. A total number of 50 articles were searched. A number of 29 articles with known concepts and a number of 25 articles with recent updates. Articles related to the aging immune system, articles related to change in the immune system when aging, articles related to aging of the immune system. Articles not related to aging and the immune system are excluded. The period or duration considered for reference articles is 2000-2020.

Immune changes with aging: Innate changes

The innate immune response is the most phylogenetically conserved protection in the animal kingdom that allows the organism to efficiently defend against an impressive number of aggressive pathogens [14]. This compartment is meant to recognize and react to the conserved pathogen-associated molecular patterns (external threats) and danger-associated molecular patterns (internal threats) by way of specific receptors that play a key role in the elimination of the aggressors [15].It appears that inflamm-aging and immunosenescence progress in parallel and form a vicious cycle. Increased

production of inflamm-aging contributed to a decrease of adaptive immune system response and eventually to immunosenescence[16].

In contrast, the decrease of the adaptive immune response reinforces the stimulation of innate immune response leading to inflamm-aging [17]. Both processes are important not only as a cause of immune change in elderly but also because of their consequences on the aging organism[18].

The interplay between aging and immune system:

It has been well established that the immune system is compromised in aged individuals. While changes occur in both arms of immunity, innate, and adaptive, studies have demonstrated that certain specific immune responses are diminished, leaving others unaffected or exacerbated [19].

This decrease in immunity that occurs for the large part, often referred to as immune senescence has been attributed to be the basis of increased frequency and severity of infections, lowered immune surveillance of malignant cells, and decreased efficacy of vaccination in the elderly [20]. The focus of a large amount of research in immune senescence has centered on T cells largely due to their role in mediating and regulating antigen-specific responses[20,21]. The central role of T cells is further underscored by fewer age-associated deficiencies in the antigen-presenting cell (APC) compartment [22]. As robust adaptive immunity relies on effective communication among T cells, APCs, and B cells, dysfunctional T cells significantly impact adaptive immune responses[23]. Functional and effective immunity to a plethora of pathogenic insults that are encountered over the lifetime of an individual is dependent on the well-orchestrated interplay between innate and adaptive immune systems.

Immunosenescence and inflamm-aging:

According to the original concept of inflamm-aging, a consequence of immunosenescence, the relatively conserved innate immune system overtakes the altered adaptive immune system in aging[23,24]. However, recent data are more in line with the interpretation that this is not a unidirectional relationship, but a mutually maintained state where immunosenescence is induced by inflamm-aging and vice versa. The main changes in the aging adaptive immune system occur in the T cell compartment [25]. There is an increase in the number of memories CD8+ T cells, which were originally considered relatively non-functional [25,26]. These cells are characterized by the loss of naïve T cell surface markers, such as CD28, CD27, and the emergence of new senescent markers such as KLRG1[27] .

It appears that inflamm-aging and immunosenescence progress in parallel and form a vicious cycle [28]. Increased production of inflammatory mediators characteristic of inflamm-aging contributes to the decrease of the adaptive immune response and, eventually, to immunosenescence[28,29]. In contrast, the decrease of the adaptive immune response reinforces the stimulation of the innate immune response as the means to protect organisms from infections in the circumstances when adaptive immunity fails leading to inflamm-aging [28–30]. Both processes are important not only as causes of immune changes in the elderly but also because of their consequences in the aging organism [31].

A dysregulatory approach integrating the immune system and other systems:

Clearly, the immune system does not exist in isolation but is influenced by and, in turn, influences many other systems such as the central and the peripheral nervous system, the endocrine system and others [32]. This fact fits perfectly with

the new approach of the study of aging which states that aging is the sum of results of the dysregulation of different systems from a normal regulatory level. This state is not necessarily identical between young and old subjects and may well reflect adaptations to intrinsic and extrinsic changes related to aging[32–34]. Thus, dysregulations are neither obligatorily detrimental nor beneficial but indicate a state of dyshomeostasis. This statement leads to the important insight that the pro-inflammatory state cannot be considered separately from the anti-inflammatory state [32,33]. In this respect, this possibility will likely be expanded and nuanced by the inclusion of other systems and cellular subsystems, e.g., mitochondrial metabolism[35] . More broadly, this approach suggests that there are clear limits to the relatively linear, pathway-based, reductionist approaches to understanding physiology in general and immunology in particular [35,36].

Convergence of innate and adaptive immunity during immunosenescence:

Aging is associated with profound changes in the human immune system, a phenomenon referred to as immunosenescence[37]. This complex immune remodeling affects the adaptive immune system and the CD8+ T cell compartment in particular, leading to the accumulation of terminally differentiated T cells, which can rapidly exert their effector functions at the expense of a limited proliferative potential [37,38].

In this review, we will discuss evidence suggesting that senescent α-betaCD8+ T cells acquire the hallmarks of innate-like T cells and use recently acquired NK cell receptors as an alternative mechanism to mediate rapid effector functions [39]. These cells concomitantly lose expression of co-stimulatory receptors and exhibit decreased T cell receptor signaling, suggesting a functional shift away from antigen-specific activation [40] . The convergence of innate and adaptive features in senescent T cells challenges the classic division between innate and adaptive immune systems. Innate-like T cells are particularly important for stress and tumor surveillance, and we propose a new role for these cells in aging, where the acquisition of innate-like functions may represent a beneficial adaptation to an increased burden of malignancy with age, although it may also pose a higher risk of autoimmune disorders [41].

Anti- aging factors involved in immunosenescence:

In the scientific community anti-aging research refers exclusively to slowing, preventing, or reversing the aging process. Pollution and stress affect the skin in detrimental ways, according to Zoe Draelos, MD, a dermatologist in practice in High Point, NC. Aging is the natural process of growing older. Yet there are many factors that play a role in whether we age gracefully or if we are the one out of two people who are faster than our biological age. More than half of the people look older than they really are because they either engage in behaviors that increase our aging, or we do not actively support a more youthful body through inaction. Knowledge is power, and the more you know about fighting the aging process, the more control you can take toward maintaining a healthier, younger body and mind.

3. Drinking & Smoking:

Smoking cigarettes can also age a person in the look of their hair. Smoking cigarettes for a long time can make an individual’s hair weaker and thinner and therefore give it the appearance of old and tattered rather than young and voluminous. Drinking a lot of alcohol can certainly age a person too. A person who drinks a significant amount of alcohol and or binge drinks quite frequently will most likely show some severe signs of aging earlier on than other people who do not follow these same drinking habits. It can also an individual’s skin look old and leave a lot of spots. Smoking cigarettes

can also age a person in his or her skin. This can cause more wrinkles and make them look older as the chemicals in cigarettes are really bad for a person to ingest and will certainly take a toll on the person's overall body in the long run.

4. Nutrition and skin aging:

Skin has been reported to reflect the general inner-health status and aging. Nutrition and its reflection on skin has always been an interesting topic for scientists and physicians throughout the centuries worldwide. Vitamins, carotenoids, tocopherols, flavonoids and a variety of plant extracts have been reported to possess potent antioxidant properties and have been widely used in the skin care industry either as topically applied agents or oral supplements in an attempt to prolong youthful skin appearance.

5. Sun, cold & moisture:

Age spots and other forms of discoloration can be seriously exacerbated by the sun's harmful UV rays. Our face that has spent years working on its tan appears heavily wrinkled and touch like show leather, once we pass the twenty-minute mark in the sun, the benefits from absorbing necessary Vitamin D are counteracted by the damage of the UV rays to the skin.Spending a lifetime in cold environments can have a similar effect. Rather than creating a tougher skin, the skin appears too thin and wrinkles develop. The same effect can be seen in people who use harsh acne treatments over a period of years.

When acne treatments dry out the skin, it can cause damage similar to the damage caused by cold and sun, creating a dry, tough, wrinkled face. When the skin's natural oils are depleted, the skin loses its elasticity and the face ages. Moisturizing daily, sometimes two and three times per day, and protecting the skin for the sun and damaging cold can combat these rather common effects on our aging process.

6. Stress:

A wide range of studies has proven that the stress caused by things like untreated depression, social isolation, long-term unemployment, and anxiety attacks can speed-up the aging process by shortening the length of each DNA strand. Every human cell has 46 chromosomes—23 come from your father and 23 come from your mother. As telomeres become shorter, their structural integrity weakens, which causes cells to age faster and die younger. In human cells, telomeres are usually single-stranded DNA that contains several thousand repeats of a simple TTAGGG sequence.

At a certain point of shrinkage, cells lose their ability to divide further. This stage is known as replicative senescence. Cellular senescence is a necessary mechanism to eliminate worn-out cells, but it also appears to contribute to premature aging and shorter human lifespans.

7. Factors that may impact of immunosenescence:

Malnutrition:

Malnutrition may be a consequence of energy deficit or micronutrient deficiency. It is considered the most relevant risk factor for illness and death, particularly in developing countries [42]. Immune cell activation and systemic pro-inflammatory mediator levels are increased in malnutrition. Malnutrition impairs immune priming by DC and monocytes

and impairs effector memory T cell function [42,43]. Malnutrition will decrease interleukin production and decrease the cell proliferation rate [42–44]. The most relevant immunological alterations found in humans or in experimental malnutrition models that affect mechanisms associated with adaptive immunity. Severe protein malnutrition in newborns and infants is clearly associated with atrophy in the so-called primary lymphoid organs like bone marrow and thymus. Consequences are devastating because these organs are generators of B and T cell repertoires. Furthermore, malnutrition clearly affects hematopoiesis, determining anemia, leukopenia and severe reduction in the bone marrow.

Diabetes Mellitus:

The increase of infections in patients with diabetes mellitus is known to depend upon an immunosuppressive condition which is brought about by impaired innate immunity and acquired immunity. Chronic hyperglycemia slows perfusion through blood vessels, causing nerve damage as time progresses. The skin, one of the key barriers in innate immunity, is no longer competent, yielding protection against trauma and inflammation [42–45]. Because of impaired nerves in the skin, the host may not notice trauma to the skin until an infection is present. As a result, skin and soft tissue infections are prominent in diabetes patients with chronic hyperglycemia. Along with poor management of blood glucose, cellulitis and diabetic foot ulcers could heal slower than desired and transition to more severe conditions such as osteomyelitis [46].

Damaged nerves are not only noted in the skin, but in other areas of the body such as the urinary tract. With damage to the nerves in the urinary tract, urine retention will breed urinary tract infections [46,47].If the pathogen is able to invade the host without the assistance of the innate immune system, an increased risk of infection is expected [48]. Hyperglycemia causes other undesirable changes in the function of the immune system such as decreased complement response, leukocyte adherence and bactericidal activity [49].

Steroid treatment:

Glucocorticoids (corticosteroids) have inhibitory effects on a broad range of immune responses. Because of their inhibitory effects on multiple types of immune cells, glucocorticoids are remarkably efficacious in managing many of the acute disease manifestations of inflammatory and autoimmune disorders [50]. While undergoing long-term corticosteroid therapy, a patient developed a clinical and immunologic picture suggestive of common variable immunodeficiency, with predominantly qualitative and quantitative B-cell abnormalities [51]. Due to the inhibitory effects on multiple types of immune cells, glucocorticoids are remarkably efficacious in managing many of the acute disease manifestations of inflammatory and autoimmune disorder.

8. CONCLUSION:

Aging is a highly complex process but an increased understanding of the process should lead to efficient treatment of many age- related diseases. There is an intricate interrelationship between inflamm-aging and immunosenescence, which are nearly identical in some ways but very different in other aspects and, occurring in concert, mutually influencing each other. Future studies are obviously necessary to elucidate these interactions and raise targets for new interventions to decrease the deleterious effects of aging and use the beneficial effects for a better health and functionspan in the elderly.

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