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The Immune System and Aging: A Review

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ABSTRACT: ***Immune senescence refers to age-related cellular and serological alterations in immune responses that influence the process of producing particular responses to foreign and self-antigens. Increasing susceptibility to infectious illnesses, worse vaccine response, and increased incidence of cancer, autoimmune, and other chronic disorders are all signs of the immune system deteriorating with age. The aging process affects both innate and adaptive immune responses; however, the adaptive response seems to be more impacted by age-related immune system alterations. Furthermore, the ethology of several age-related illnesses (atherosclerosis, Alzheimer's disease, osteoporosis, and diabetes) has been linked to a persistent low-grade inflammatory state in the elderly. However, some people reach late years without significant health issues, which is referred to as healthy aging. Immune system dysfunction seems to be reduced in this group, most likely owing to unknown genetic and environmental causes. The goal of this study is to outline what is currently known about how the aging process affects the immune system.***

KEYWORDS: Aging, Immune System, Immune Senescence, Innate, Adaptive Responses

1. INTRODUCTION

Aging is a complicated process that has a significant impact on the immune system. Higher susceptibility to infectious illnesses, worse vaccine response, increased incidence of cancer, autoimmune, and other chronic diseases defined by a pro-inflammatory state, such as atherosclerosis and diabetes mellitus, all indicate the immunological system's deterioration with age. Immune senescence refers to age-related cellular and serological alterations in immune responses that influence the process of producing particular responses to foreign and self-antigens. The immune system is a complex system in which a variety of different cells throughout the organism interact with one another, either directly or through a variety of soluble mediators, to achieve a comprehensive defence of the organism against ‘‘foreign attacks" while maintaining control of proper cell proliferation within the body.

The immune system's processes are classified into two categories: innate and adaptive. The anatomical and physiological barriers, as well as the unspecific cellular response mediated mostly by monocytes, natural killer cells, and dendritic cells, make up the innate response. T and B cells mediate the adaptive response, which is an antigen-specific response. The aging process affects both components of the immune response, although the adaptive response seems to be more impacted by age-related immune system alterations[1]. The goal of this study is to outline what is currently known about how the aging process affects the immune system.

Methods

A comprehensive review of research concerning immune system aging was conducted. The following keyword-based search strategy was intended to find publications that explain a connection between aging and the immune system: (immune senescence or aging) and (immune system or immunity or immunological), followed by a particular search for each main component of the immune system. This technique was modified and used to a number of popular Internet search engines, the MEDLINE database, and the Cochrane Controlled Trials Register. There were no restrictions on language or time[2]. A hand-search of the reference lists of chosen review articles was used to complement this search.

Theories and causes of immune senescence

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Autoimmunity, immunodeficiency, and immunological dysregulation are the three main hypotheses proposed to explain immune senescence. According to the immune insufficiency hypothesis, as people become older, their immune systems become less capable of defending the body against external invaders, causing negative effects. Various changes in the immune system occur with age, breaking the control between multiple components of the immunological process, suggesting the gradual death of bodily cells, according to the immune dysregulation hypothesis.

From the standpoint of evolution

The immune system is constrained by evolutionary forces. Humans used to live for 30–50 years, but today they live for 80–120 years. This is taking longer than expected. This situation indicates an antigenic load spanning decades of unanticipated evolutionary exposure. Pleiotropy that is antagonistic Natural selection has favoured genes that provide short-term advantages at the expense of later-life degeneration[3]. As a result, the immune system is likely to have been chosen to assist people just until reproduction, after which biochemical processes may continue without any previous selection pressure to enhance an individual's life. This theory is supported by the fact that thyme involution occurs early in life.

From an endocrine standpoint

The connection between the immunological and endocrine systems is highlighted by many common mechanisms: first, cells in both the immune and endocrine systems contain receptors for cytokines, neuropeptides, and neurotransmitters. Second, both systems have immune–neuroendocrine products, and third, endocrine mediators regulate the immune system, while immunological structures mediators may impact the endocrine system. Steroid hormones may influence gene expression in cells that contain receptors for these hormones, which may alter immunological response. Furthermore, immune cells may bind to steroids, growth hormone, estradiol, and testosterone through receptors. IL-1, tumour necrosis factor, and IL6 may block the hypothalamic–pituitary–thyroid axis, and the hypothalamic–pituitary–adrenal axis can affect immune activities by inhibiting immune cell development, differentiation, and proliferation.

Because Gonadotropin-releasing hormone is involved in the development and modulation of the immune system, the hypothalamic–pituitary axis may also influence immunological function. The natural reaction Barriers of the skin and mucous membranes with both a barrier and a mechanistic role, the skin and mucous membranes are the first line of defense against infections[4]. Dermal and subcutaneous atrophy occur when skin cell renewal diminishes, sweat and sebum production decreases, and structural changes such as flattening of dermoepithelial junctions, depletion of Langerhans cells and melanocytes occur with age. Changes in ciliary beat frequency in mucous membranes, where ciliated cells play an essential role by physically eliminating pathogens, are disputed, with some studies showing no alterations with age and others reporting a decreased ciliary beat frequency.

Ultrastructural anomalies may also be discovered. The first line of defence against infections that penetrate mucosal surfaces is secretory IgA, the major immunoglobulin in secretions, in combination with anatomical and mechanical barriers. Secretory IgA levels were shown to rise with age until 60 years old, then fall somewhat after that, at least in saliva. Dendritic cells are a kind of cell that may be found in the Dendritic cells (DCs) are important for pathogen detection, phagocytosis, antigen processing, migration to regional lymph nodes, priming of

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naive T cells, and the control of B and NK cell responses. They are the first to detect the presence of a pathogen and serve as a link between innate and adaptive immune responses. DCs are divided into two types: myeloid-derived DCs and lymphoid-derived DCs. Healthy aging seems to have little effect on the number of DC in the body, but it does reduce the number of particular subsets such as Langerhans cells in the skin and plasmacytoid DC – and in the presence of chronic illnesses.

DCs detect conserved pathogen related molecular patterns utilizing pattern recognition receptors, particularly Toll-like receptors, whose function has been found to be impaired in the aged, in order to successfully perform their duty as sentinels in the organism's entrance sites. The phosphoinositide 3-kinase signalling pathway is also a detrimental influence on phagocytosis and migration in old age. Although most studies indicate a decreased inflammatory response that may be linked to a reduction in IL-15, tumour necrosis factor (TNF)-a, and IFN-a expression in response to viral infections and vaccinations, the consequences of age on the inflammatory response and T cell priming by DCs remain unclear. Natural killer cells (NK cells) Natural killer cells are essential components of the innate immune system. They detect and destroy cells missing MHC class I molecules without being sensitized or activated by other cells, and they secrete a range of cytokines to help sustain innate and adaptive immune responses. Cell cytotoxicity and cytokine secretion are carried out by two subpopulations of NK cells: CD56dimCD16 NK cells, which are truly cytotoxic cells with low cytokine production, and CD56brightCD16- NK cells, which are less differentiated cells whose main response upon activation is cytokine and chemokine production.

It is generally acknowledged that the number of NK cells in the elderly increases[5]. This rise seems to be the consequence of the organism's mature cells accumulating, resulting in an increase in the CD56dim population. Despite this, the increase in NK cells is not linked to a rise in overall cytotoxicity. It's possible that the increase in NK cells is a compensatory mechanism for the lower per-cell cytotoxicity that seems to be caused by lower perforin production. Although no age-related changes in the expression of adhesion or chemokine receptors have been found in human research, NK cell migration has been demonstrated to be altered in mouse models. In addition, NK cell cytokine production seems to be decreased, as does their proliferative response to IL-2 activation.

Neutrophils

Neutrophils are short-lived phagocytic cells that circulate in blood arteries until cytokines and chemokines, primarily IL-1 and IL-8, attract them to the infection site. They are the first line of defence against microbial and parasite infections, and they work via three major mechanisms: phagocytosis, reactive oxygen species production, and degranulation, as well as neutrophil extracellular traps. The quantity of neutrophils does not seem to be affected by age in most studies, but their capacity to extend their life span in response to survival signals generated at the infection site appears to be reduced. Chemotaxis causes endothelial cells to adhere to each other and migrate via them into the afflicted region[6]. Adhesion and migratory processes seem to be unaffected by age, however it is uncertain if chemotaxis is altered. In terms of phagocytosis, the majority of writers believe that in the aged, phagocytic function and the intracellular respiratory burst required to kill germs are decreased. A reduction in CD16 expression seems to be responsible for the impairment in opsonized bacteria phagocytosis and superoxide production. It's yet unclear how aging influences the formation of neutrophil extracellular traps.

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Macrophages

Macrophages are tissue-resident phagocytes that are generated from circulating monocytes and, like DCs, have a large number of Toll-like receptors, allowing them to recognize pathogens with conserved pathogen-associated molecular patterns. Immune, endocrine, and central nervous system interactions. They have paths that cross each other. TNF, tumour necrosis factor; VIP, vasoactive intestinal peptide; ACTH, adrenocorticotropic hormone; CRH, corticotrophin releasing hormone; TNF, tumour necrosis factor; VIP, vasoactive intestinal peptide Tissue macrophages, which synthesize pro-inflammatory cytokines and chemokines including TNF-a, IL-1, IL-6, and IL-8, play an essential role in neutrophil recruitment. They may also process and deliver antigens to T cells, as well as contribute in the adaptive immune response's control. In elderly individuals, macrophages produce fewer cytokines like TNF-a and IL-6 in response to TLR1/2, but no other TLR that may be responsible for less powerful neutrophil and other cell recruitment. In addition, TLR-induced B7 expression is reduced in the elderly. They also exhibit a change in the expression of MHC class II molecules, which has yet to be determined but may lead to a worse T cell response. Although these results have yet to be reproduced in humans, studies on mouse models have revealed that macrophages from elderly people express less MHC class following stimulation with IFN-gamma II, have impaired phagocytosis, and have a reduced capacity to generate reactive oxygen species[7].

The adaptive response

Progenitors of lymphocytes Hematopoietic stem cells are mostly located in the bone marrow and are essential for maintaining a steady supply of both myeloid and lymphoid progenitors for a healthy immune response. The HSC's proliferative ability declines as it ages, and a shift toward the generation of myeloid progenitors occurs. Shortening of telomeres, epigenetic alterations caused by reduced DNA methylation in HSCs, and changes in the HSC niche, including the cytokine milieu, have all been suggested as possible reasons for the shift toward the myeloid series. B cells are a kind of cell that is found .the generation of particular antibodies in response to a specific antigen is the primary activity of B cells, and this function is critical for a successful response to bacterial infections and vaccination. Somatic hyper mutation of immunoglobulin genes in the germinal centre of secondary lymphoid tissue produces high-affinity-specific antibodies, which are then secreted by professional antibody-secreting plasma cells that move to the bloodstream. The overall number of B cells seems to decrease with age, which is consistent with HSCs' decreased capacity to produce new B lymphocytes. In addition, as individuals become older, their B cell repertoire becomes less diverse, as shown by a reduction in naive B cells (CD27; few somatic mutations in immunoglobulin genes) and an increase in memory B cells (CD27; numerous somatic mutations).

Apoptosis resistance is enhanced in these memory B cells. Furthermore, several studies indicate an aging-associated B-cell subtype that increases with age and responds to innate but not adaptive immune cues, but further research is required to fully understand their function in people. Antibody production is influenced by age, just as it is by changes in B cell subsets[8]. When it comes to vaccinations, older individuals have a delayed reaction, less clonal growth of plasma cells, which corresponds with a reduction in immunoglobulin synthesis, and lower antigen affinities. Despite the fact that fewer plasma cells are produced, their individual antibody secreting activity seems to be intact, as does the somatic hyper mutation machinery. Furthermore, when a primary antibody response is required in the presence of novel antigens, the elderly show a delayed response with lower levels of high-affinity antibodies, which is

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subsequently compensated by clonal growth, which may be explained by a reduction in the native B cell pool.

Globally, those with somatic mutations consistent with their production mainly by memory B cells dominate the circulating immunoglobulins, resulting in an increase in autoantibodies. In elderly individuals, the humoral response's capacity to generate antibodies capable of opsonizing germs for neutralization by phagocytosis is also reduced, which goes hand in hand with the reduction in high-affinity antibodies. With aging, it appears that three major impairments affect B cells: a reduction in the number of native B cells, resulting in a reduced capacity for response to new antigens; a reduced clonal expansion capability of memory B cells, which correlates with a lower level of circulating antibodies after contact with a previously known antigen; and functionally impaired antibodies with lower affinities.

T cells are a kind of white blood cell that T cells are distinguished by the presence of TCRs and may be divided into two groups based on whether they express CD4 or CD8 on their cell surfaces. CD4 cells are mostly regulatory cells that identify antigens provided inside Class II major histocompatibility complex (MHC) molecules, while CD8 cells are primarily cytotoxic cells that recognize antigens presented within Class I MHC molecules. In both adaptive and innate immune responses, both roles are critical.

The absolute number of T cells decreases with age, and this reduction, like that of B cells, has a greater impact on the native subset. T cells differentiate in the thymus, resulting in the generation of CD4 or CD8 native cells, which are subsequently sent to the periphery. T cells rearrange their TCR genes throughout maturation, resulting in DNA pieces called T cell receptor excision circles, which have been utilized as an indirect indicator of thymopoietic capacity[9]. Thyme involution is extensively documented in the literature and is thought to be the primary mechanism through which the population of native T cells decreases with age. CD4 and CD8 cells are affected differentially by this decrease, with a larger shrinkage in CD8 cell counts and a better maintained population of naive CD4 cells. Functional abnormalities, such as antigen-independent activation and proliferation rates, have been reported with the numeric deficiency in natural T cells. When confronted with a novel antigen, these cells that retain their original phenotype are less capable of generating an effective response.

Inflammation

Increased levels of circulating cytokines and pro-inflammatory markers define inflammation, which is a persistent state of low-grade inflammation that occurs as part of the aging process. Many age-related illnesses, such as atherosclerosis, Alzheimer's disease, osteoporosis, and diabetes, are linked to it. TNF-a, IL1 and IL6 are among the pro-inflammatory cytokines that seem to play a key role. Anti-inflammatory cytokines like IL-10, on the other hand, seem to suppress these pro-inflammatory states in healthy aging[10].

2. DISCUSSION

Immunosenescence, or the age-related decrease in immunological functions, is partly to blame for the increasing frequency and severity of infectious illnesses, as well as the poor immunization effectiveness in the elderly. Immunosenescence is marked by a reduction in cell-mediated immune activity as well as humoral immunological responses. Age-related alterations in the innate immune system coexist with age-related abnormalities in T- and B-cell activity. The processes and effects of age-related immunological changes, as well as their implications for health in old age, are discussed in this study. Antibody titters after traditional

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booster vaccinations for tetanus or TBE are similarly lower in the elderly than in the young, decrease quicker, and the function of the antibodies generated is also reduced. Improved vaccination methods, new adjuvants, and new vaccines that target the aging immune system will assist to overcome Immunosenescence limits and guarantee an adequate immunological response in the elderly.

3. CONCLUSION

Immuno-senescence is a complicated process that affects the immune system as a whole and has an impact on the organism's capacity to react to infections effectively. There is no one deficiency to blame; rather, it is a multilayer disorder that affects people differently. As a consequence, older individuals are more susceptible to infections, have lower vaccine responses, and have worse reactions to recognized and novel antigens. Furthermore, older people have a persistent low-grade inflammatory state, which has been linked to the etiology of many age-related illnesses. Furthermore, an age-related deterioration of the immune surveillance function has been linked to an increased incidence of cancer. However, some people reach late years without significant health issues, which is referred to as healthy aging. Immune system dysfunction seems to be reduced in this group, most likely owing to unknown genetic and environmental causes.

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