IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 7 Ser. 6 (July. 2024), PP 24-30
www.iosrjournals.org

C-Reactive Protein And The Process Of Inflammaging In Cardiovascular Disease: The Influence Of Environment In Health Across Generations

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Abstract
The authors portray the principles of immune-metabolic interaction, and elaborate on the molecular mechanisms by which diet, host genome, gut microbiome, and immune responses interwine to influence metabolic homeostasis throughout the years until old age. In this perspective, the discussion revolves around the clinical aspects by which immune activation may predispose to pathological metabolic states, as well as how the environment, genetics, and microbiome may regulate complex immune-metabolic interactions and propensity to develop metabolic diseases. In this review, it is presented integrated research from many fields – psychosocial, neuroimmunology, environmental, and genomics – to elucidate how early life stress and behaviours may influence immune system processes to increase vulnerability and risk for inflammation-derived chronic illness, as well as the role of C-reactive protein (CRP) and its relation between chronic inflammation in the aetiology of cardiovascular diseases (CVD). Based on medical literature, the suggestion is that stressors occurring during childhood to older age program a defensive immunology phenotype by increased inflammatory reactivity and thereby be at risk of chronic diseases and its conditions. This information is used to propose an integrated, multi-disciplinary understanding on how these factors interact and cause health disparity across domains based on socioeconomic and behaviours, that could be targeted to burden disease risk, and improve lifespan health.

Keywords: *immune system; chronic inflammation; immunosenescence; cardiovascular diseases; C-reactive protein; immune-metabolic interactions; lifespan health.*

Date of Submission: 08-07-2024 Date of Acceptance: 18-07-2024

I. Introduction

Inflammation has been implicated in the aetiology of a wide range of diseases of aging, including diseases of the cardiovascular, metabolic, musculoskeletal, nervous, and immune systems [1,2].

Inflammaging is an important link among obesity, insulin resistance, aging, and age-associated diseases such as cognitive impairment, atherosclerosis, cancer, and autoimmunity[3,4]. Recently, there have been major developments in understanding the cellular and molecular bases, and genetic and epigenetics changes, in the innate and adaptive immune system during aging[5].

The aging process is characterized by a chronic inflammation ('inflammaging")[6,7,8]. Aging represents a paradox of immunodeficiency and inflammation and autoimmunity. Over the lifespan there are changes in the architecture and functioning of the immune system often termed "immunosenescence"[9,10,11]. Several factors contribute to inflammaging, including polymorphisms in pro-inflammatory genes, chronic stimulation of immune cells (viruses such as cytomegalovirus), changes in gut microbiome, and increased permeability from the intestine. Senescence induces the accumulation of differentiated B, T and Non-Killer cells (NK), with dysregulated function through the activation of pathways integrating senescence and energy-sensing signals[12-16].

II. Pathophysiology And Immune System

The immune system has a remarkable ability to remember and respond to different stimuli, leading to heterogeneity in immunesenescence[12,17]. This variety results from differences in type, dose, intensity, and temporal sequence of stimuli to which each individual is exposed.

Immune cells of the innate and adaptive immune systems infiltrate insulin responsive tissues, and incite inflammatory responses. Immune cells (macrophages, T,B, NK cells, and neutrophils) have been implicated in adipose tissue inflammation and insulin resistance[18,19,20]. Inflammation leads to increases in pro-inflammatory molecules (TNF-α, Interleukin-1β – IL-1β, Interleukin-6 - IL-6, Interferon-γ – INF-γ, inflammatory adipokines, chemokines, and free-fatty acids (FFA), as shown in Figure 1[21-26].

Macrophage infiltration within the adipose tissue is considered a major driver of inflammation, due to secretion of pro-inflammatory cytokines and chemokines involved in the recruitment of immune cells to the adipose tissue[27,28]. However, adipocytes also secrete pro-inflammatory mediators (cytokines, chemokines, and adipokines) and in larger amounts compared with immune cells. Macrophages in the adipose tissue are almost exclusively type 1 (M1), they depend on glycolysis for their inflammatory function, and their stimulation in the adipose tissue induces glucose transporter expression and glucose intake and utilization[29-32]. In macrophages, the inflammasome NLRP3 activates caspase 1 and the secretion of IL-1β, which is directly toxic to pancreatic β-cells and induces insulin resistance. Increased inflammasome activity has been reported in monocyte-derived macrophages from type-2 diabetes (T2D) patients (Figure 2)[33-36].

Interferon-γ (IFN-γ) – is the Th1 cytokine – induces macrophages and T-cells to secrete chemokines, which recruit immune cells to the obese adipose tissue. Interferon-γ facilitates the M2 to M1 polarization and decreases insulin receptor and glucose transporters[37,38].

Obese and T2D patients have alterations in the composition of their microbiome, with reduced beneficial bacteria. Moreover, obesity and hyperglycaemia have direct influence on antibody production, and Immunoglobulin G (Ig G) secretion from inflamed visceral adipose tissue modulate the function of resident macrophages[13,33,39,40,41,42].

Recent researches have implicated inflammatory processes in the pathophysiology of a wide range of chronic degenerative diseases, although inflammation has long been recognized as a critical line of defence against infectious disease. The impact of aging and cytomegalovirus (CMV) infection on immune cell function - for example –, the response to influenza infection and vaccination, and how the current understanding of aging and CMV can be used to design a more effective influenza vaccine for older adults which will also need to focus on generating appropriate T cell responses[10,17,43,44].

The aging process link the inevitable decline in body systems and physiological processes of an organism's existence. This process involves immune and metabolic changes – which is considered physiological -, but it also predisposes to aging-related pathological conditions including neurodegenerative diseases, sarcopenia and cardiovascular diseases (Figure 3)[45,46]. The term "inflammaging" describes a low-grade pro-inflammatory shift in innate and adaptive immunity, with increased pro-inflammatory cytokine levels (TNF-α, IL-6) and elevation of anti-inflammatory agents (cortisol, hypothalamic-pituitary-adrenal axis)[47,48]. Another hallmark of "inflammaging" is the decline of autophagy, leading to increase in ROS production and inflammasome activation, which contribute to obesity and insulin resistance. With the increase in life expectancy and the proportion of elderly population in Westernized societies, alleviating the burden of metabolic morbidity associated with aging will become an inevitable challenge to health economies[50-54].

Emerging evidence shows considerable variation and plasticity in human immune development and function, and it points to aspects of the nutritional, microbial, and psychosocial ecology in infancy and early childhood as determinants of an individual's immunophenotype. An ecological, developmental approach recognizes that the immune system develops and functions in whole organisms that are integral parts of their environments. To understand the relation between ecological factors and inflammatory phenotypes and its research on the regulation of inflammation is the aim of this review[34,55,56,57].

The generally harmful effects of chronic inflammation are not limited to those mediators produced as a result of chronic infection. The immune and inflammatory impact of obesity on many health parameters, including decreased and dysregulated B cell function and antibody production as well as inflammaging[58-60]. Not only does immune dysregulation contribute to inflammaging, but chronicity of inflammatory exposure, as opposed to the necessity of acute inflammation for immune response generation, also negatively influences immune function[61,62,63].

This article illustrates only some of the many facets of immune aging, a rapidly developing field now being increasingly recognized as central not only to immune function *per si* in the elderly, but to their general condition of health or frailty.

The ecological contingency in immune development and maturation depends on interaction with antigens from the environment to adapt an individual's specific lymphocyte group to the local disease ecology[4,5,6,64]. For example, low levels of infectious exposure in infancy are associated with increases in Th2 cytokine production and total Immunoglobulin E (Ig E) concentration, promoting allergic, atopic, and autoimmune diseases later in life. Another example is the hygienic hypothesis, showing that microbial exposures in infancy leads to development of immune regulatory networks in ways that are important for limiting immunopathological processes, showing important rules for the human gut microbiota[3,17,65].

III. C-Reactive Protein And Inflammaging

This concept of inflammation as a chronic phenomenon contributing to diseases of aging is new. Inflammation has been understood as a critical component of innate immune defences against infection and injury. Acute activation of inflammatory process after pathogen exposure is rapid – within hours – whereas specific immune process -mediated by T or B lymphocytes – take several days to come on line. C-reactive protein (CRP) is detected in blood circulation, and its concentration increase as part of the acute-phase response to infection, becoming a nonspecific indicator of clinical or subclinical infection. CRP plays a role in activating complement, promoting phagocytic activity, and opsonizing bacteria, fungi, and parasites[66,67,68].

C-reactive protein is a prototypical acute-phase protein and commonly measured in clinical and epidemiological setting, as this biomarker may contribute to the assessment of chronic inflammatory process in a wide range of diseases of aging, including CVD, T2D, metabolic syndrome (MS), and late-life disability. According to guidelines, the cutoff point of CRP >3 mg/L identifies individuals at high risk for CVD[66,67,69].

Therefore, there are two perspectives among inflammation and diseases: the acute phase emphasizes short-term elevations of CRP as adaptive responses to pathogenic challenge to protect from infectious disease; on the other hand, the chronic low-grade inflammation perspective contributes to development of aging diseases, like CVD.

IV. Immune Responses And Its Impact Of Human Behaviour And Environment

Immune-related processes impact metabolic processes through multiple mechanisms:

A. Prenatal and early postnatal nutritional environments have lasting effects on human immunity. Infants who are born small for gestational age are less likely to respond to vaccination in adolescence, have higher levels of IgE, and produces lower concentrations of thymic hormone – thymopoietin -, important for cell-mediated immunity[70].

B. Psychosocial factors also are important part of the ecology of human immune function. The impact of stress on immunity in infancy is well-established and is associated with reduced cell-mediated immunity and increased inflammation in adolescence and adulthood[37,49,71]. Low socioeconomic status early in life predicts high levels of CRP in adults, as well as increased proinflammatory and decreased anti-inflammatory gene expression.

C. People living in industrialized environments enjoy unprecedented access to high-caloric foods, low physical exertion and energy expenditure, and reduced varieties of microbial diversity in sanitation and hygiene[71,72]. Saprophytic mycobacteria, Lactobacilli, and many Helminthes common in soil have been part of the human environment and are treated as harmless by human host represent disappearing classes of microorganisms[73,74].

D. Frequent but transient with microbes in local environment may be important in the regulatory method, and it may influence the structures of resident microbial communities in the human gut and on mucosal and skin surfaces[75,76]. The cellular mechanisms involve regulatory T cells and the balance of pro- and anti-inflammatory cytokine production and related intracellular pathways. Epigenetic modifications to genes involved in these methods represent a viable molecular mechanism through which microbial exposures in infancy may have a durable impact on inflammatory phenotypes.

The microbiome may also be linked to the aging process. Gut dysbiosis was associated with a decline in intestinal barrier integrity, negatively correlated with levels of pro-inflammatory cytokines (IL-6, IL-8) and markers (TNF-α, CRP)[45,61].

V. The Immune-Metabolic Systems

The relationship between immune and metabolic systems is not only confined to resource sharing, but also includes interfaces in which cellular stress driven by metabolic perturbation also manifests as an inflammatory response aimed at restoring homeostasis by adjusting broader biological functions, including endocrine and metabolic process.

Below, examples of genetic, dietary and environmental factors that impact immune-metabolic intersections, and how they may affect homeostasis and the propensity for metabolic disorders are listed:

1. Diet: diet modulates immune activity in multiple ways. Food ingredients may impact immunity either by interacting with immune cells via receptor-mediated signalling or via interaction with gut microbiota by modulating metabolites, affecting metabolic homeostasis. Vitamin D is obtained from diet in its inactive form, followed by biochemical conversion involving liver, skin and kidneys, including hepatic hydroxylation into 25(OH)D3 followed by renal hydroxylation into 1,25(OH)D3 the most active vitamin D isoform[77]. Vitamin D regulates mineral metabolism and maintains a healthy mineralized bone structure, as well as its hydroxylation take place enzymatically in dendritic cells, B cells, and T cells, leading to regulation of cellular differentiation and proliferation. It also plays an important role in maintaining immunologic homeostasis and gut barrier integrity, with consequent impact on metabolic homeostasis[74,77].

The metabolism of lipids leads to the production of fatty acids that contribute to a major source of biological lipids, playing a role in structuring cell membranes and providing energy stores. Consumption of high saturated fatty acid diet leads to adipocyte and circulating immune cell activation, resulting in TNF-α and pro-inflammatory cytokine secretion. This subclinical inflammation involves adipose tissue recruitment of pro-inflammatory M1 macrophages, which contributes to insulin resistance. In contrast, polyunsaturated fatty acids (derived from fish and plant-derived foods) are utilized in the synthesis of compounds such as steroid hormones. Omega-3 - polyunsaturated fatty acid – is available in Mediterranean diet and acts in suppressing inflammation by interacting with adipose tissue immune cells[35,78]. Lipoxin, resolving and protectin are also metabolites of polyunsaturated fatty acids, and have been implicated in the resolution of inflammation due to their anti-inflammatory properties[1,2,75].

Dietary fibers metabolized by gut microbiome into short-chain fatty acids mediate immune responses, such as cytokine and chemokine production in intestinal epithelial and mononuclear cells, neutrophil chemotaxis, immune cell differentiation, anti-inflammatory processes, and inflammasome activation. In parallel, short-chain fatty acids supress appetite, regulate leptin production and lipolysis in adipocytes, and protect against insulin-mediated fat accumulation. The absence of dietary fibers, short-chain fatty acids are depleted in the gut and the epithelial barrier integrity is not warranted, resulting in systemic endotoxemia, leading to adipose tissue inflammation and insulin resistance[17,62,63].

2. Genetics: in addition to diet, genetics constitute an important contributor to induction and maintenance of immune-metabolic homeostasis. Gene approaches identify genetic contribution to metabolic diseases, e.g. immune-cell receptor CD44 as a gene implicated in T2D, regulating immune cell migration and is involved in adipose tissue inflammation, with consequent insulin resistance[5-7,39,42].

3. Epigenetics: it constitutes an important mechanism link, by which environment impact host gene expression, and contribute to immune and metabolic system cross-regulation. Obesity is an example; it involves polarization of adipose tissue macrophages (ATMs) from anti-inflammatory macrophage-2 (M2) to a pro-inflammatory M1-like, in addition to altered methylation of T cells and macrophage[11,12,19,20].

The gut microbiome plays an important role in epigenetic alterations both to metabolism and immunity through short-chain fatty acids (STFAs), which act to regulate the expression of immune-related genes and attenuate inflammation.

The metabolic syndrome (MS) is comprised of obesity, T2D, hypercholesterolemia, non-alcoholic fatty liver disease, and their complications. Systemic low-grade inflammation in the liver, muscle, and adipose tissue is a major contributor to the development of obesity and insulin resistance[1,2,9]. Insulin resistance serves as a transient mechanism, deviating serum glucose to leucocytes required for preservation of homeostasis and tissue repair upon acute infection. Long-term consequences may be metabolically detrimental. Cytokines and chemokines (IL-6, IL-1β, TNF-α, macrophage migration inhibitory factor) are released by adipocytes and immune cells, contributing to the emergence of obesity[58,69].

The importance of the above interactions between the immune and metabolic system is exemplified in states of metabolic disturbances from over- or under-nutrition to overt manifestations of the metabolic syndrome. Inflammation is a contributing or a regulating factor and involves immune signalling either in haematopoietic-derived immune cells or in tissue resident cells.

The intestinal microbiome is a key regulator of immune and metabolic functions and suggested to be a central factor to inflammation in metabolic syndrome. Obesity is associated with reduced microbial diversity and altered microbial composition[63,74].

While the trialogue among immunity, metabolism and microbiome in metabolic syndrome has not been completed understood, it seems to involve increased gut permeability, allowing for a closer interface between the microbiome and the host. Enhanced influx of bacterial organisms into the portal circulation may lead to inflammatory activation deteriorating metabolic diseases[75,76].

VI. Treatment

Inflammatory and metabolic signals are closely inter-related in multiple facets and suggest that anti-inflammatory strategy may be useful in treatment of insulin resistance and metabolic disturbances. Multiple anti-inflammatory treatments improve metabolic diseases, such as blockade of inflammatory cytokines (TNF-α and IL-1β); blockade of IL-1β improves insulin secretion and glucose homeostasis besides reduces haemoglobin A1c (glycated haemoglobin) and fasting glucose levels.

A healthy lifestyle has been recognized as the most effective way to maintain health against inflammaging, such as adequate nutrition intake, moderate exercise[71,72], and good mental health can delay aging[50,64]. Minerals (zinc)[79], probiotics (Lactobacillus var. plantarum C29) and vitamins (C, E)[80]. Consumption of polyunsaturated fatty acids reduces levels of inflammatory cytokines; vitamins like C and E can effectively improve the function of immune cells in the elderly. Minerals like zinc increase näive T-cells and improve homeostasis of Th1 and Th2 cells[19,79].

VII. Conclusion

The investigation of the mechanisms whereby inflammation and immune activation disrupt a functional immune response adds novel insights to the understanding of the relationship between inflammation and long-term metabolic disease outcome and opens new ways for effective therapeutic interventions. Detailed profiling of immune markers, host genetics, epigenetics, and microbiome configurations could be of use for prophylaxis and early diagnosis in metabolic diseases. More holistic approach that consider multiple factors may be necessary to fully understand the complexity of immunosenescense and inflammaging.

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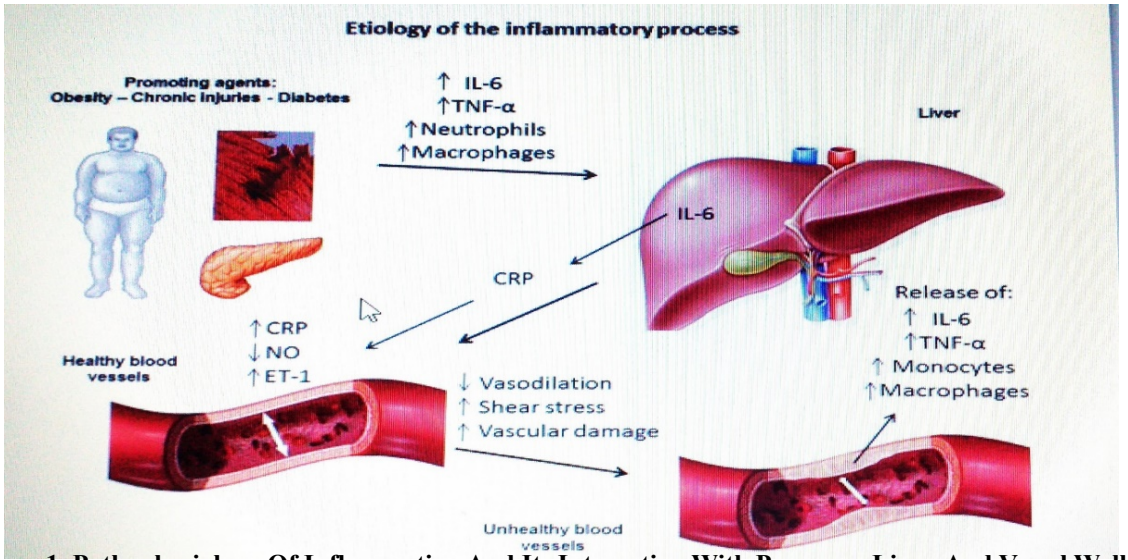

Figure 1. Pathophysiology Of Inflammation And Its Interaction With Pancreas, Liver, And Vessel Wall. Chronic Inflammation Increases Inflammatory Cells Migration, Leading To Augmentation Of C-Reactive Protein (CRP In Response To Interleukin 6 (IL-6), Which Provoke Vascular Damage And Diminish Vasodilatation. TNF-A, Tumour Necrosis Factor-Alfa; IL-6, Interleukin 6; CRP, C-Reactive Protein; NO, Nitric Oxide; ET-1, Endothelin1. From Camm Et Al, 2019.

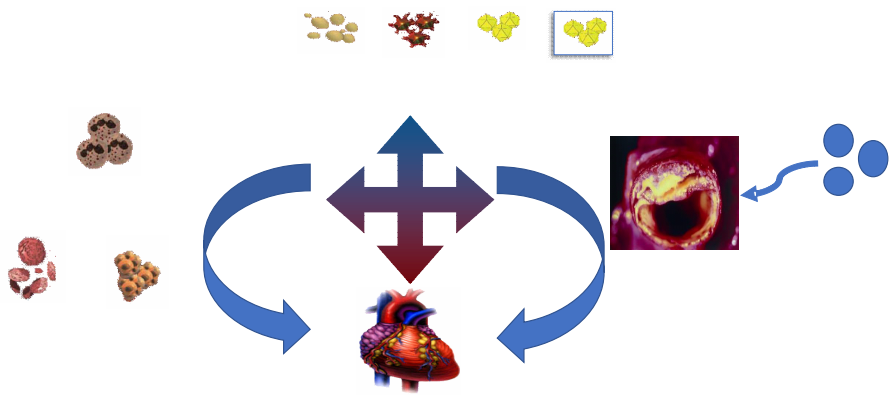

Figure 2. The Outburst Of The Inflammatory Process Within The Atherosclerotic Plaque, Leading To Plaque Rupture With Thrombosis And Coronary Artery Disease. Patients In Whom Plaque Instability Is Caused By Inflammatory Outburst Present Hyperreactivity To The Inflammatory Stimulus Represented

By Myocardial Necrosis , Which Promotes Plaque Instability . The Intensity Of The Inflammatory Surge Predicts Short And Long-Term Outcome. IL1β, Interleukin 1β; IL-6, Interleukin 6; IL-1R, Interleukin 1 Receptor; IL-6R, Interleukin 6 Receptor; CRP, C-Reactive Protein; VEGF, Vascular Endothelial Growth Factor (Permitted By The Author).

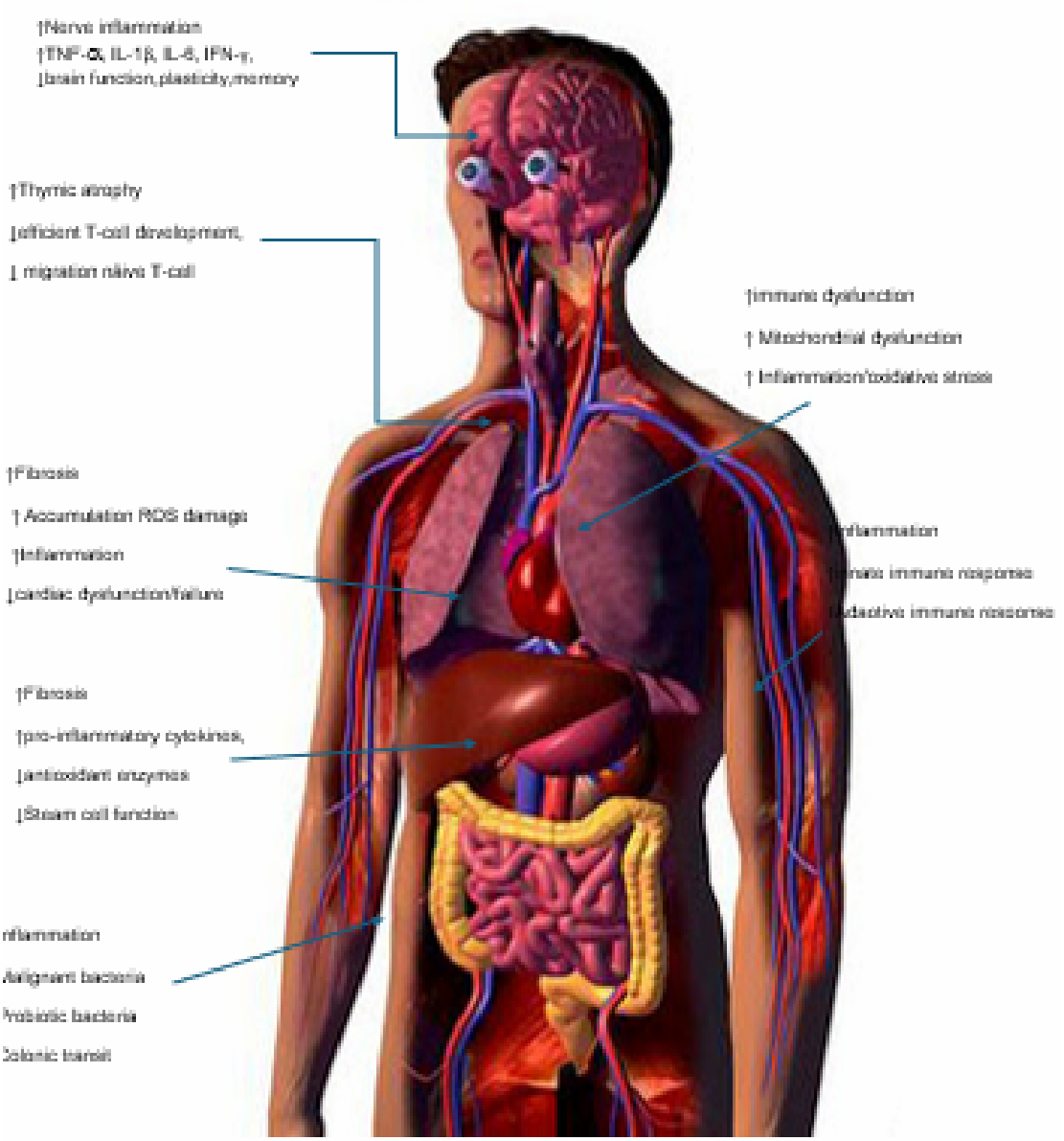

Figure 3. Aging Manifests As A Decline In Organ Function And Facilitates The Increase Susceptibility To Chronic Diseases. Organs Are Divided Into Immune And Sterile Organs. Functional Changes Are Shown In Respective Organs. (By The Author).