CONCEPTUAL STUDY

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Role of immunosenescence and inflammaging in life style diseases

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ABSTRACT: The immune system in our body is the most complex one designed to fight against harmful substances and foreign bodies. Inflammation is the first response of the immune system to any foreign body or organism. But these protective responses can turn pathological resulting in cellular senescence. This pathological response is now understood as the basis of a large number of diseases having unexplained pathology. Immunosenescence and inflammaging are the new terms which explain age related increase in pro inflammatory markers and which act as a cause for diseases of elderly, like cardiovascular diseases, autoimmune disorders and different carcinomas. The concept of *agni* and *vyaadhikshamatwa* helps to explain the process of ageing and autoimmune disorders. Different concepts of *agni, vyaadhikshamatwa* and effect of treatment modalities like *deepana, paacana, snehana, sodhana* etc., should be considered in these spectra of diseases.

Keywords: Immunosenescence, Inflammaging, Lifestyle disorders, Agni, Aama.

INTRODUCTION

The immune system in our body is a complex system of organs, cells, proteins and that protects the body against infections, harmful substances and cell changes that could hamper the normal functioning of body.[1] Functions of immune system include an orchestrated effort by the immune cells to fight infections, neutralize harmful substances and fight non-infectious diseases. Even though its function is to keep us healthy, mistakenly it damages the healthy cells in our body. Inflammation is the first response of the body's immune system to a foreign body or an injury. It is an essential phenomenon of body's healing process and occurs when inflammatory cells travel to the place of injury or foreign body. If the inflammatory cells stay too long, it may lead to chronic inflammation.[2] This chronic inflammation can be a causative factor for most of the diseases of elderly like infections, cancer, autoimmune diseases and chronic inflammatory diseases. Inflammaging is a new term for this phenomenon put forward by recent researchers which can be defined as an age-related increase in the levels of pro-inflammatory markers in blood and tissues, and is considered a major risk factor for multiple diseases that are highly prevalent in elderly individuals.[3] The elevated levels of blood inflammatory markers cause high susceptibility to chronic morbidity, disability and mortality. It is also a risk factor for cardiovascular diseases, diabetes mellitus, cancer, depression, dementia etc.[4]

In the classical textbooks of *ayurveda*, the concept of *agni* is explained whose malfunctioning results in the accumulation of *aama* and this concept well explains the chronic low-grade inflammation and resulting autoimmune disorders. Immunity is well explained under the term *vyaadhikshamatwa, ojus* and *bala*. *Vyaadhikshamatwa* is defined as the power of resistance capable enough to prevent the occurrence and progression of a disease. Different types of people have different levels of *vyaadhikshamatva* depending on *prakrti*, diet,

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lifestyle etc. Recent research works also explain the possibility of modulation of immune response by use of *rasaayana* drugs.[5]

Aim: This work is intended to explain the scope of *vyaadhikshsmatwa*, concept of *agni*, *aama* and the application of *deepana-paacana* drugs, *dinacarya, rtu-sodhana, snehana and rasaayana* in most prevalent diseases due to immunosenescence and inflammaging. An attempt to understand the possible *sampraapti* and effective *cikitsa* is also made here.

Materials and methods: References were collected from the classical textbooks of *ayurveda* and recently published articles on the topic. Materials from textbooks of basic physiology and pathology were also used for analysis.

Immunosenescence

The term senescence literally means growing old. During ageing, the immune system undergoes several changes collectively called immunosenescence. Compared to healthy individuals the aged shows a decline in many immune parameters. The bulk of these changes happens not only in ageing but also in a chronic mild inflammation of cells as a result of stress. Immunosenescence can be considered as a process of immune dysfunction that occurs with ageing and causes remodelling of lymphoid organs and thus immune function of the elderly. [6] Immunosenescence and inflammaging are said to perform an important role in the pathophysiology of autoimmune diseases, cancer and chronic inflammatory diseases. One of the salient features of immunosenescence is T cell output decline which leads to the production of senescence associated secretory phenotype, increased glycolysis and reactive oxygen species. Understanding the molecular mechanism in immunosenescence is inevitable for the development of effective treatment protocols and immunotherapies and thus solving the existing dilemma regarding autoimmune and other related pathologies.[7]

Molecular mechanism in immunosenescence

The most major important component of adaptive immune system is T-cells. They perform their function by directly killing infected host cells, activating other immune cells and producing cytokines.[8] There are two types of T cells – Naïve T cells and Memory T cells. Naïve T cells are phenotypically smaller and they enter the lymphoid tissue by crossing the walls of some specialised venules name as High Endothelial Venules. They move repeatedly from the blood stream to the lymphoid organs and back to blood making contact with thousands of Antigen Presenting Cells in the lymphoid tissue. Naïve T cells also act as precursors of effector T cells and memory T cells. The naïve T cells get activated in the presence of IL 4 produced by a variety of innate cell types in response to parasites. These activated inexperienced T cells induce T cell differentiation into Th2 subsets which in turn generate an inflammatory response to eliminate antigen. Functional naïve T cell output reduces after puberty. This may be due to involution of thymus gland after puberty. This reduction in functions of naïve T cell results in increased proliferation of existing T cells and eventually phenotypic conversion of naïve T cells to virtual memory cells. In contrast to the inability of naïve T cells to get activated, properties of memory T cells increases during early age and remains stable throughout adulthood. After adulthood the proportion of memory T cells starts to show senescent changes.[9]

Memory T cells are antigen specific T cells that remain for a long term after an infection. There are two types of memory T cells – Central memory T cells (T_{CM}) and Effector memory T cells (T_{EM}). The Central memory T cells are confined to secondary lymphoid tissues and are enriched for CD^{4+} T cells. Effector memory T cells, being short lived are confined to peripheral compartments and are enriched for CD^{8+} T cells [8]. On aging, the

CD^{28+} cells are replaced by highly differentiated CD^{28-} T_{EM} cells. These cells are characterised by decreased proliferative capacity, shortened telomere and enhanced cytotoxic activity. Progressive shortening of telomere results in senescence, apoptosis and oncogenic transformation of somatic cells. [10] CD^{28} loss is thus associated with increased chance of infections and weakened immune response to vaccination in elderly.

Inflammaging

Acute inflammation is the first physiological response to an injury or an infection which is followed by a cascade of events for wound healing and remove invading pathogens. Even though acute inflammation is a beneficial process transient immune responses with ageing leads to chemical, physical and nutritional triggers and it becomes low grade chronic causing tissue dysfunction and degeneration. Chronic inflammation occurring as a result of continued presence of this initial trigger may initiate ageing process which is harmful to health. In normal cases also aging is associated with low grade sterile inflammation and this inflammation has been considered as one of the seven pillars of aging. This age related sterile chronic low-grade inflammation is known as inflammaging. Aging here is not necessarily chronological but also biological aging which was thought to be caused by continuous antigenic load and stress. But since the last two decades, a new hypothesis has been explained with a complex phenomenon of cellular senescence.[11] A heightened inflammatory stage can be produced by the following factors.

1. Dysfunctional mitochondria – continuous dysfunction of mitochondria can initiate an inflammatory response which in turn may lead to autoimmune cardiovascular and neurological diseases.
2. Defective autophagy–autophagy is the mechanism by which damaged cell organelles, denatured proteins and pathogens are removed by lysosomal degeneration pathway. Defective autophagy plays an important role in innate and adaptive immunity and thus initiate inflammation.
3. Stress in endoplasmic reticulum – leads to the accumulation of unfolded proteins and thus destruction of the cell.
4. Defective ubiquitin – the main function of ubiquitin is to regulate protein homeostasis and thus manage immune response angiogenesis, cell proliferation and DNA repair.
5. Activation of DNA damage response
6. Senescent T cells and their senescence associated secretory phenotype – this phenotype is associated with senescent cells which secrete high levels of inflammatory cytokines and immune modulators.
7. Age related changes in the composition of gut microbiota[12]

Aging at cellular level can be explained by the UPR (Unfolded Protein Response) pathway. At cellular level, protein synthesis and folding is the function of endoplasmic reticulum. Folding is the process by which a newly synthesised protein entering the endoplasmic reticulum is subjected to a series of modifications and encounters a set of folding enzymes and thus become biologically active to perform its function. A number of factors like hypoxia, glucose deprivation, oxidative stress, viral infections, high fat or cholesterol and mutations may lead to ER stress and accumulation of unfolded protein in the endoplasmic reticulum. Even though these misfolded proteins are inactive, their accumulation in the ER can cause stress response.[13] If this stress response persists for a long time it will lead to apoptosis and thus destruction of the cell. Thus, inflammaging results in increased levels of pro-inflammatory markers in blood which plays an important role in the pathophysiology of multiple diseases that are highly prevalent these days.

Immunosenesence and inflammaging in *ayurveda* perspective

Vyaadhikshamatwa is the umbrella term for all immune functions of the body. It varies from individual to individual depending on the body constitution (*Prakṛti*), diet, exercise, life style etc. According to Chakrapanidutta, the term *vyaadhikshamatwa* can be interpreted as *vyaadhi-bala-virodhitatwam,* that is bodily facter against the strength and virulence of disease and *vyadhi-utpaadaka-pratibandhakatwam,* the capacity to prevent the causes of disease.[14] This could be understood by explaining basic metabolism of our body. *Agni* plays an important role in the normal functioning of the body metabolism. This functioning of *agni* can be explained at the cellular level also. Mitochondria, the energy source of our cell can be functionally related to *agni.* When this *agni* is impaired, there is an accumulation of *aama*, the unfolded proteins which lead to *srotorodha* and finally destruction of these cells. Improper metabolism leads to the accumulation of *aama* both at the cellular level and gross level.This impaired *agni* is considered as the root cause of all diseases. This accumulated *aama* needs to be cleared out of the body through periodic *ṣodhana* and *agni* should be maintained by proper *deepana paacana*.[15]

Immunosenescence and cancer

One of the major risk factors for development of cancer is cellular aging, to be more specific inflammaging. Inflammaging plays a significant role in the pathophysiology of cancer in almost all stages from cellular proliferation to metastasis. Molecular and cellular pathway is involved in the age related chronic inflammation and it triggers the metastasis including continuous pro inflammatory signalling pathways.[16] Inflammaging is characterised by the presence of a systemic proinflammatory state with increased concentration of circulating interleukins like IL6, IL1, TNF α and inflammatory markers like CRP. Cancer occurs not only in the sites of chronic inflammation but also in a proinflammatory micro environment. Mechanism by which a cell sense the cell damage or pathogen can be explained by UPR pathway which leads to the production of cytokines, free radicals and hormones which in turn alter the cellular physiology. Accumulation of DNA damage promotes cellular senescence which actively participates in tumorigenesis. Development of a tumour can be arrested by cytotoxic innate and adaptive immune cells. As a tumour develops to a clinically detectable stage, cancer cells undergo a different mechanism by which tumoricidal attack is avoided. At different phases, cancer related inflammation contributes to genomic instability, genetic modification, progression of cancer cell proliferation, stimulation of angiogenesis and thus cancer dissemination. Primary and metastatic tumours are complex ecosystems which contain the inflammatory immune cells. This ecosystem also contains accessory non neoplastic cells which fuels tumour development.[17] Latest studies have accepted the fact that at least 25 % of cancers are associated with chronic inflammation. For example, HPV induced inflammation in cervical cancers, Helicobacter pylori in gastric cancer increased risk of colorectal cancer by immune dysregulation in IBS. Diet also plays an important role in induction of cancer associated inflammation. The non-human form of sialic acid in red meat can be incorporated into human cells and recruit inflammatory cells.[26]

Immunosenescence and cardiovascular diseases

Inflammaging is a risk factor for cardiovascular diseases. In older age humans there is a tendency of high levels of pro inflammatory markers in cells and tissues. Genetic variants also affect the levels of pro inflammatory markers. Increased levels of IL-1β, IL6, TNFα lead to cellular senescence including impaired mitochondrial function, oxidative stress, DNA damage and telomere shortening and thus closely related to cardiac

pathologies. Obesity, hypertension, diabetes, smoking and atherosclerosis also act as risk factors for cardiac inflammation. In addition to the pro-inflammatory cytokines contributing to cardiac aging, there is also a large number of pro inflammatory macrophages infiltrated into the myocardium of healthy person. [20] Cardiomyocytes require a high energy supply and sufficient amount of ATP is necessary for their contractile function. 5AMP activated protein kinase (AMPK) is the key energy sensor in the cardiac myocytes. AMPK gets activated when adequate ATP is not synthesised and leads to the stimulation of catabolic process in the myocardium. AMPK switches off many energy consuming activities like protein and lipid synthesis and activates energy releasing processes like autophagy. Stress related activation of AMPK also initiates the same process. The precise mechanism of age-related AMPK activation is unknown but the role of protein phosphatases, disturbance of Ca^{2+} homeostasis and activity of inhibitory upstream kinase has been considered. Mitochondrial dysfunction is also considered as one of the major reasons for cardiac aging. Mitochondrial dysfunction leads to accumulation of unfolded proteins, damaged DNA and thus creates an oxidative stress within the cell.[21]

Immunosenescence and autoimmune diseases

Changes occur in the immune system, during the aging that lead to an increased chance of autoimmune diseases. This is because of increased reactivity to self-antigens and loss of tolerance. Elderly people show a tendency of generalised systemic inflammation along with aggravating degenerative diseases which in turn increases the risk of developing autoimmune diseases. With increased inflammatory cytokines and chemokines like TNF-α, C- reactive protein, IL-8, MCP1 etc., there is also an age associated alterations in T cell cytokine profile contributing to the development of autoimmune diseases. Some autoimmune diseases are not limited to old age but also occur very frequently in younger patients, which can be attributed to altered T and B cell function. Autoantibody production such as rheumatoid factor, ANA, antiphospholipid can be closely related to clinical characteristics of elderly and also to patients with autoimmune diseases.[23] One of the major causes of autoimmunity is telomere abnormality. Telomere length and cellular aging are inversely related. Cells having very short telomeres enter senescence rapidly. Telomeres are located at the end of chromosomes which prevents cleavage of DNA through cell repair and thus protects the DNA. Telomeres also provide chromosomal stability and prevent chromosome binding and breaking during mitosis.[24] Genetic background of the individuals plays an important role in this pathogenesis. Lymphocytes, especially CD4 lymphocytes are involved in synovial tissue inflammation. These aid the production of proinflammatory cytokines and autoantibodies. Lack of telomerase activity in CD4+ naïve T cells is the key factor.[25]

DISCUSSION

The science of *ayurveda* always aims at maintaining the homeostatic state of the body. Thus there is a need to understand the *sampraapti* of life style diseases from this point of view. In ayurvedic classics *granthi* and *arbuda* are the names given to non inflammatory and inflammatory swellings respectively. Pathogenic injuries to the sixth layer of skin, *mamsadhaatu* and *medodhaatu* as a result of lifestyle errors, *viruddhaahaara*, poor hygiene leads to derangement of *doshas* and manifestation of *arbuda*.[18] Uncontrolled proliferation can be explained by defective *vaata* and *agni* which is in turn due to *aama* and *kapha*. Thus, an interplay of all the three *doshas* and *rakta* can be understood in pathology by the uncontrolled mitosis, metabolic error, accumulation of cells and angiogenesis of proliferated tissues respectively. A practical approach to treat this dreadful disease

needs to be explored. By following *pathyaahaara*, periodic *sodhana* and adopting a healthy life style one can prevent the low-grade inflammation and cellular senescence to a certain extend. [19]

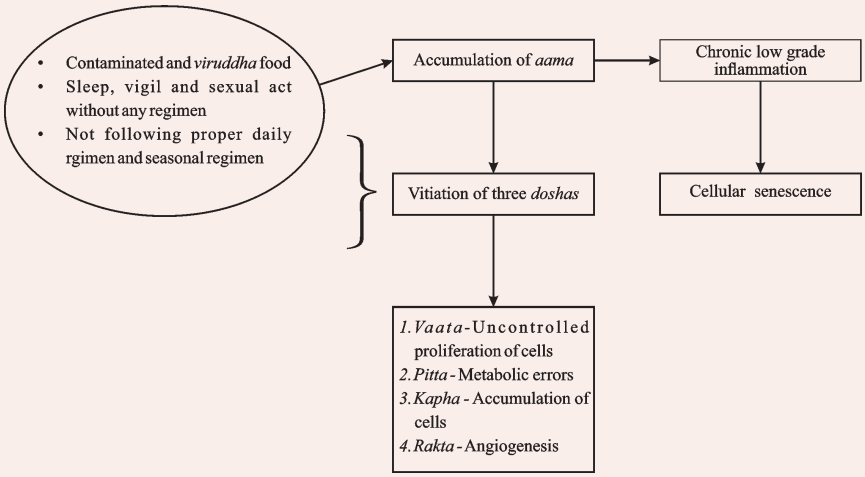

Figure 1

Diseases of heart are grouped under *hṛdroga* and are explained to have their *adhishṭhaana* in *koshṭha*. The predominant *dosha* is *vaata, so* that pathogenesis of *gulma* and *śoola* is also need to be considered. *Hṛdaya* is one of the *trimarma* and any abnormality should be addressed with priority. [22] In *ayurveda,* cardiovascular diseases are also explained in the contexts of *rasa-vaha srotas* and *praaṇa-vaha srotas and rakta-vaha srotas.* Thus pathology of *hṛdroga* starts in the *koshṭha*. Liver also plays a role by facilitating digestion through digestive enzymes produced which can be considered as *pitta*. When there is any derangement in this physiology, there is accumulation of *aama, kapha-pitta dushṭi* along with *vaata-dushṭi* and *rakta-dushṭi,* manifesting as *hṛdroga*. Hence correction is to be begun at *koshṭha* level. Following proper regimen as explained in *dinacarya*, drugs having *rasaayana* property and *deepana paacana* actions in diet, periodic *śodhana* etc., can prevent the accumulation of *aama* to a certain extend.

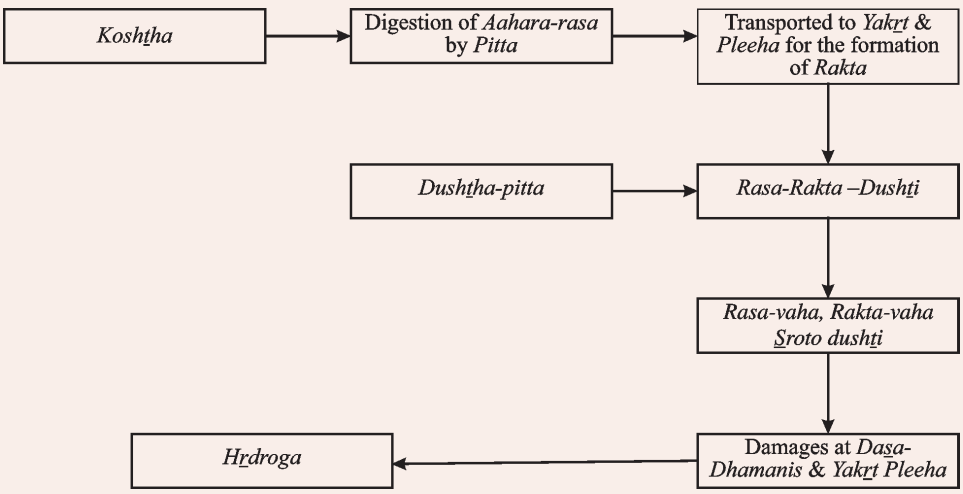

Figure 2

Involvement of *manas* is also considered owing to the involvement of *saadhaka-pitta*. So therapies like *yoga*, *praan<u>a</u>ayaama* etc and *sadv<u>r</u>tta* have to be practised to mitigate *manodoshas*.[29]

In ayurvedic perspective, accumulation of toxins or *aama* in the body and impairment of *agni* at the cellular level play a key role in the pathogenesis of autoimmune diseases. A variety of drugs explained in our classics like *aamalaka, gu<u>d</u>ooci, pippali* and combinations like *triphala*[28] are proved to have immunomodulatory effect. Repeated *<u>s</u>odhana* also helps to clear out continuously forming antibodies and use of *rasaayana* helps in preventing recurrence of the pathology. Hence, *deepana paacana* drugs having *rasaayana* properties like *gu<u>d</u>ooci*[27], *punarnava* are usually used in the treatment of common autoimmune disorders.

CONCLUSION

A large number of diseases which were earlier considered as having unexplained pathology is now understood as the manifestations of a defective immune system. From an ayurvedic view this can be observed in two pathways, *vyaadhi-utpaadaka-pratibandhakatwam* (prevent the onset of diseases) and *vyaadhi-bala-virodhitatwam* (arresting the progression of diseases). Prevention of diseases can be considered primarily for an individual as well as for a community. For a community, the concept of *janapadodhwamsa* can be considered. If these principles are not followed and disease get manifested, then the first step is to arrest the progression of such diseases. Drugs having *deepana-paacana* properties can be used to digest the accumulated *aama*. Once an autoimmunity sets in over the period of time, there is a low grade chronic inflammation. So there is a need of repeated *sneha-sveda* followed by *<u>s</u>odhana* to expel out this *leena dosha*. Continuous scavenging of free radicals by periodic *<u>s</u>odhana* helps to maintain a healthy cellular environment. After clearing the *srotases* and attaining *agni-bala,* proper *rasaayana* medicines can be administered. Thus, by properly assessing the stage of *sampraapti* and applying appropriate treatment modalities these pathologies can be prevented and the progression of such diseases can be arrested.

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