



Aging Immunity Microbiome Axis

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Abstract: Human ageing influence immunity and modify microbiome. Ageing scientific workers have made three questions as; why ageing, why do we age, and how do we age. They evolve theories in trying to answer them. The concepts of; ageing, immunity and microbiome were elucidated. Ageing affect immunity, ageing affect microbiome. Mutual communications between these elements were bidirectional. The objective of the present opinion paper was to suggest and prove for an "Ageing-immunity-microbiome axis" through review current relevant publications and showcase analysis for an age human population. This suggested axis pathway starts as low grade inflammation, chronic low grade inflammation, inflamm-ageing, inflamma-immuno-ageing, immune senescence then microbiome modifications. Each of the tripartite elements of the axis affect and affected by the other via multiple bidirectional cross-talk communications.

Keywords: Age, ageing, axis, immunity, inflammageing, inflamma-immuno-ageing, microbiome.

INTRODUCTION

Ageing is a phase of human life cycle forming a part of the paradigm of life extremes. It may be defined as "Getting Old" [1]. Immunity is the natural built-in ability of human being to resist infection, infestation and cancer. It can be ramified into; innate, innate trained, immune cross-roads and adaptive immunity [2]. Microbiome is an immune and physiologic organ that contained the cultivable and non-cultivable balanced; virome, bacteriome, and mycome that may inhibits in or on any of human healthy body compartments. Though in cases of; infection, infestation, vaccination and neoplasms unbalancing "dysbiosis" which appeared as shifting in composition, diversity and function [3]. Axis is a functional concept that encompasses a complex interplay where the ageing-immunity-microbiome are interconnected regulatory system describing the interconnected and mutual influences of ageing process, the immune system and microbiome on each other and overall health [4]. The objective of the present opinion paper was to suggest and prove through review current relevant publications and show case analysis to human age population.

AGEING

Why Ageing [5, 6]

Aged peoples formed a reasonable percentage of the major human populations all over the world. They hold the position of a valid, educational, experienced and natural historic and heritage live reserves of the nations. Though they may face solitary, isolated, poor and weak human day life, in some eastern societies and be housed in an ageing hostile systems.

Why and How We Age

Theories that tried to explain, why and how do we age, are competing each other making it in a way or other unlikely that more than one of them could be the true. Among these theories are of biological issues [7] as;

- **Programmed Longevity**

It considers ageing to be a result of a sequential switching on and off of certain genes with senescence being defined as the time when age associated deficits are manifested.

- **Endocrine Theories**

It is being in hold where biological clocks act through hormones to control the pace of ageing.

- **Immunological Theories**

immune theories state that the immune system is programmed to decline overtime.

- **Error Theories**

- Free radical, gradual accumulation of free radical as oxidative cellular damage.
- Nucleic Acid Errors, Errors occur in the transcription of DNA are perpetuated and eventually lead to system malfunction. The organisms ageing attributed to these errors.
- Cross-linking, Glucose binds to protein in presence of O₂, once bind, protein becomes impaired and unable to function efficiently.
- Neuroendocrine, upon ageing the secretion of hormones by human endocrine glands declines and their effectiveness is also reduced due to receptor down grading.

More details on benefits and defects of experimental ageing tempts on laboratory mice made by ageing scientists are tabulated in Table 1.

Table 1: Experimental lab animal studies on ageing process [7]

Theories /Hypothesis	Proves	Benefits	defects
Cross-linking	Cross-linking of glucose with protein or DNA in presence of O ₂	Extended life span, cross-linking contribute to ageing	Malformed proteins and DNA
Evolutionary Senescence	Hazardous environment favor early reproduction and short life span. Safer environment favor slow reproduction long life span	Conditional, Extension of life span.	Early reproduction, short life span. Slow reproduction long life span
Single Gene Mutation	Single gene mutated affect number of finite pathways	Extend life span	Animals inactive with reduced fertility and inherent defects
Non-programmed ageing	Animals feed on standard low ration% goes different in final fate	Increase life span	Some died other got cancer, but with heart safe mode of action

Caloric Restriction	Laboratory animals on balanced diet 30-40% less calories	Increase life span in rodent retard all almost age related changes	Test animals are thin, cold, stunted, some - time sterile
Genome maintenance	Decline in DNA repair and accumulation damaged DNA in cells of elderly than in young	DNA repair system found in young cells and weak or absent in elderly	Sex cells passing genetic defects to the progeny somatic cells not

Ageing Concept

It is a normal state in the life cycle of human in which the subject is being getting old. It is mostly associate with structural changes and functional decline in the major biological activities and landmarked by weakening of normal day life affairs [1].

Features

Biological feature associated with human ageing are briefed in Table 2.

Table 2: Biological Changes Associated with Human Ageing*

Parameters	Biological Changes
Size	Height and weight decrease in both man and women due to losses in muscles and bone after age 60
Metabolism	Gradual diminution in metabolic rate after age 30
Skin and hair	Loss of subcutaneous fat; appearance of wrinkles pigmentation. Graying and loss of hair of all body sites. Nails thicken.
Heart and cardiovascular functions heart	Some thickening of heart muscle, wide spread of cardiovascular disease
Organ physiology	The functions of kidney, lung and pancreas diminish. Atrophy skeletomuscular system. Decline in reproductive functions. Impairment in senses
Neurobiology	Shrinkage of brain, learning and memory impaired. Some degree of senile dementia after age 70.

*Adopted from Clark, [8].

IMMUNITY [2, 9, 10]

Stimulants

Infectious agents antigens, haptens, adjuvants, vaccines and nonspecific immune-stimulants

Immune System

The structural elements of human immune system are; lymphoid organs, mononuclear cell system, complement and kinins, acute phase reactants and the genetic component. While functional are as systemic and mucosal immune systems.

Antigen Potentials

Antigens, haptens-carrier combinations can act as; mitogens, immunogens, allergens, anergens, toleragens, and /or immunosuppressents. These potentials are mediated by

specific few amino acid group or carbohydrate surface side chains or internal located give their; valency, specificity and immunogenicity.

Innate Immunity

It is a; general natural built in, gene encoded and functions in first exposure to invading pathogens and cancer. It shows limited specificity due to the specific recognition ability of TLRs on surface of phagocytes. It is promoted by a set of humoral and cellular components.

Innate Trained Immunity

Innate trained immunity represents a phenomenon where exposure to certain microbial pathogen results in the priming of the innate immune system to initiate a more potent and rapid response upon subsequent encounters with different pathogenic microbes. Unlike adaptive immune memory supported by B and T cells, trained immunity introduces a paradigm shift demonstrating that innate immune cells have memory like properties. Such properties are encoded by epigenetic mechanism [9].

Immune Cross-Roads

Some innate humoral and cellular factors take part in the adaptive immune mechanisms in one hand and a part of adaptive immune mediators and cells take part in innate immune mechanisms "Immune Cross-Roads" [10].

Adaptive Immunity

Antigenic stimuli may initiate changes in naïve B and naïve T cells to be activated through the two signal transduction pathways to be, a committed effector, memory or regulatory lymphocyte subsets with their subsequent mediator production, antibodies and /or cytokines. Adaptive immunity requires twice or multiple antigen exposure with their marked specificity and frequent shared specificity.

Features of Immune-ageing

In the immune sense ageing associated with structural reduction in immune cell niches in human lymph nodes. Though in immune functional sense there were functional reduction in antibody levels, cytokine levels and programmed cell death. This corresponds to increase in numbers of autoreactive lymphocytes and increase in term of concentration and titers of auto antibodies. Together with appearance of inflammaging, immune-inflammaging, immune-senescence and microbiome modifications as dysbiosis and associated immune dysregulation.

As well as weak immune response to vaccines, vulnerability to infectious diseases and reduction in immune resilience ability, Table-3 [11-18].

Table 3: Immune and Molecular Features of Human Ageing [11-18].

Immune Features
<ul style="list-style-type: none"> • reduction of B cell niches in lymph nodes • Reduction of T cell niches in lymph nodes • reduction of T and b cells in in circulation • reduction of NK cells in circulation and lymph nodes • decrease in antibody levels and concentrations in circulation and at mucosal surfaces • decrease of cytokine levels in circulation and at mucosa • immune dysregulation • reduction in immune resilience ability • Microbiome dysbiosis • Increase in autoantibodies and autoreactive cells in circulation • Brook of tolerance
Molecular
<ul style="list-style-type: none"> • Increase of telomerase activity in chromosome tips • decrease of telomeres length in chromosome tips.

MICROBIOME

The normal cultivable and non-cultivable genetic determined; viruses, bacteria and fungi inhabiting external or internal human body compartments are termed as microbiome. Under normal immune homeostasis microbiome is balanced. While, under pathologic conditions as; ageing, menopause, infection, infestation, vaccination and/or cancer, microbiome undergoes unbalancing in composition, diversity and function, "dysbiosis". It holds the position of life long partner of immunity [3, 19-21].

CORRELATION BETWEEN AGEING, IMMUNITY AND MICROBIOME

As we age, the immune system functions are declined, a process termed immune-senescence. This is characterized by a weakened ability to positively respond to infection, vaccination, neo-plasims, a loss of tolerance and persistent low grade inflammation called inflammageing. The accumulation of immune cells that secrete the proinflammatory cytokines contributes to the evolution of ageing. As a human being body ages, the gut microbiome undergoes significant changes in composition, diversity and function which often leading to dysbiosis, an imbalance in composition and limitation in diversity. This commonly involved in reduction of beneficial short chain fatty acid, or amino acid producing bacteria which paralleled with increase in potentially harmful or pro-inflammatory bacteria which can be influenced by diet, physical activity and medication. Microbiomes are crucial for development and regulation of the host immune system. Microbial metabolites like SCFAs and amino acids help in activity of the immune cell decline in immune functions [12-24].

AXIS PATHWAY

Axis is a functional term involved mutual bidirectional cross- talk between its related elements. The ageing-immunity- microbiome axis is a bidirectional regulatory system describing the interconnected and mutual influences of the ageing process, the immune system and the microbiome or each other and overall health. This axis plays a critical role in the development of the age related diseases and has emerged as key factor in health

ageing and longevity. The axis starts with low grade inflammation, chronic low grade inflammation, inflammageing, inflamma-immuneageing, then immune senescence and dysbiosis of microbiome. The three elements are mutually cross talk to each other by this we term it as multiple bidirectional mutuality, [25-30].

AXIS CONSEQUENCES

The consequences of immune dysregulation associated with microbiome dysbiosis and ageing are; reduction in vaccine efficiency due to decline in immune function, vulnerability to infection, rise up of metabolic diseases such as obesity, cardiovascular diseases, neurodegenerative disorders like Alzheimer and Parkinson's disease. As well as musculoskeletal diseases like that of osteoporosis and sarcopenia [3, 4, 13-18]

SHOW CASE ANALYSIS [16]

Introduction

Human ageing and longevity have a strong familial and genetic traits. The characteristics of the ageing process, nature of immune function and gut microbiome dynamicity were the aims of the present show case.

Program

The 16S rRNA and metagenomics sequencing were made for 32 longevity families to reveal the synergist changes between the ageing immune decline and the microbiome associated changes. The test longevity families include three generations of; centenarians, elderly and young groups for comparison.

Results

Centenarian subjects have shown reduced levels of inflammatory and anti-inflammatory cytokines except elevated levels of IL10 in centenarians compared to young and elderly groups. Gut microbiome have shown increase in anti-inflammatory bacteria and enriched probiotic microbial species especially *B. fragilis*. Together with depleted associated microbial amino acids and increase damaged connections among bacteria in centenarians compared to young and elderly groups.

Conclusions

Reduced levels of inflammatory cytokines indicate chronic low grade inflammation. Reduced levels of inflammatory and anti-inflammatory cytokines compared to young and elderly indicates immune decline in centenarians. Increase in the anti-inflammatory IL10 cytokine stands as a cytokine balancing response in centenarians and mediate critical balance between health and disease. *B fragilis* was suggested as beneficial bacterium important in repair of the impaired immune functions.

Axis Analysis

Chronic low grade inflammation indicated by reduced inflammatory and anti-inflammatory cytokine responses in centenarians and immune-ageing. High IL10 levels indicated cytokine balancing response. Microbiome modification as increase of anti-inflammatory bacteria and enrichments of probiotic microbial species indicated dysbiosis, paralleled by the noted immune dysregulation. These are the pillars of the axis pathways.

CONCLUSIONS

The suggested ageing-immunity-microbiome axis proved by the facts presented in the aforementioned paragraphs and showcase analysis of centenarian families.

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