 ISBN 978-602-60569-3-1

THE PROGRESSIVE LOW CHRONIC INFLAMMATION ON ORAL TISSUES IN ELDERLY

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INTRODUCTION

Aging is a normal process, as inevitable biological phenomenon. Generally, this process characterized by a decrease in the ability of resolution, regeneration, and reparation of cell and tissues, So, those cells and tissues cannot function properly and its will grow up and die.[1] WHO reports that the population of elderly people worldwide increases by 1.7% annually, whereas the population of people aged ≥ 65 years old increases by 2.5%. WHO classified the elderly based on their chronologic/ biologic state in 4 groups: (1) the middle age ranged 45-59 years old, (2) the older/elderly age ranged 60-74 years old, (3) the advanced old age ranged 75-90 years old, and (4) the very old age over 90 years old. Generally, elders ≥ 65 years old have health problems as effects of aging process. That means they need to have a special concern about their health condition include in dental care.[2,3]

Low, systemic and progressive chronic inflammation in elderly age is called inflammaging. This condition can occur as the effects of injury on cells and tissues.[4,5] There are some factors that cause injury on cells, such as; hypoxia, chemical materials (toxins, drugs), physical agents (mechanical trauma, temperature, sudden changes in atmospheric pressure, radiation, electrical potency), microbiology agents (virus, microbes, fungi), immune system disorder, genetic disorder, or malnutrition. When the cells got injuries, there are some possibility reactions on cells and tissues, e.g. retrogressive reaction, progressive reaction; and adaptation reaction. The main cause and the response towards inflammaging that linked to illness are still unknown.[6]

INFLAMMAGING MECHANISM IN ELDERLY

The main cause of inflammaging that can be detected is accumulation (i) endogenous host-derived cell debris (cells, organelles, and macromolecules damaged); (ii) cellular senescence and senescence-associated secretory phenotype/ SASP [7]; (iii) immunosenescence by persistent infections [8]; (iv) waste product of body, which has local effect and systemic; and (v) increasing of coagulating system.[9]

Inflammation is a very complex responses to many stimuli, in which many different cells types and secreted factors orchestrate protective immunity, tissue repair, and resolution of tissue damage.[6-9] Chronic inflammation is strongly connected with each of these aging phenotypes. The inflammatory mediators are IL-1β, IL-6, IL-8, IL-18, TNF-α, and CRP. Although it is not clear what causes age-associated chronic inflammation, possible mechanisms include a disregulated the signal transduction pathway, NF-kB pathway and signal transducer and activator of transcription/STAT in chronic inflammatory cells. One or both of these proteins regulate many genes that encode the synthesis of pro-inflammatory cytokines. NF-kB, organize most of the genes included SASP. NF-kB is also shown encouraging some aging phenotype and inflammasome. The activation of inflammasome is very important in the inflammaging and pathogenesis of various diseases of elderly people. [10-15]

Inflammaging will reduce the ability of inflammatory cells to destruct microbes and or its products, that causing low level of chronic inflammation. Immune cells and non-immune active aging cells (cell senescence) destruction induces the production of pro-inflammatory cytokines, which modulates senescence-associated secretory phenotype/SASP, regulation of apoptosis, inflammatory responses, and alters the phenotype surrounding cells.[16,17]

The senescence cell known as stimulator of diseases through SASP. SASP roles in modifying microenvironment and alter the function of normal cells or transform surround cells.[13,14] Accumulation of senescence cells can be found in adipose tissue, particularly visceral fat in obese individuals. Fat is the source of pro-inflammatory cytokines. Therefore, the massive alteration in the distribution, composition and functions of fat, effects clinically on some age-related disease. These cells will continue to accumulate during the aging process, and resulting pathological alter in cells and tissues. Therefore, destruction of senescence cell can prevent age-related disease.[19-20]

Mitochondria also play an important role in inflammaging to activate Nlrp3 inflammasome. Nlrp3 inflammasome is a multiprotein complex that can activate pro-caspase-1.[18] When cell injury occurs,

by synthesizing and secreting cytokines pro-inflammatory IL-1β, IL-6, IL-8, IL-18, and TNF-α. Activation of Nlrp3 inflammasome induces excessive reactive oxygen species/ROS in mitochondria, accumulate senescent cells, and decline in autophagy with age. and caused mitochondrial damage. [21-23]

Anabolic signaling disorder may occurred because of pro-inflammatory cytokines such as IL-6, TNF-α, CRP, insulin-likegrowth factor-1/IGF-1, and distruption of erythropoietin signal and protein synthesis.[20,24] This metabolic disorder resulting cells lose its ability to regenerate and repair. This age disorder can occur through alter deoxyribonucleic acid (DNA), which led to a genetic disorder. In addition, disturbance of synthesis and enzyme activity induce reduce cytoplasmic protein, and increase metaplasmic protein (collagen and elastin), decrease amount and structure of mitochondria, degeneration lysosomal leads to hydrolysis cells, Nissl reduction, the collection of chromatin, increase pigment lipofuscin and protoplasm vacuolization. Eventually, number and function of cells and tissues will decrease. [25,26]

Accumulation of waste products from the body cells, such as endogenous host-derived cell debris (brokencells, organelles and macromolecules), free radicals, metabolites and protein of high-mobility group box 1/HMGB1 (endogenous destroyer which may destroy active molecules in innate/natural immunity). Metabolites such as extracellular ATP, fatty acid, uric acid crystals, ceramides, cardiolipin, amyloid, succinate, lipid peroxidized, advanced glycation end-products (AGEs), N-glycans alteration, and protein of high-mobility group box 1/HMGB1 (including Nlrp3 inflammasome) serum; acts as a danger sign on the elderly people tissues, resulting in chronic inflammation and mal-adaptive, which are susceptible to diseases.[6]

As known, loss of lubricants can also cause dysfunction in various tissues and organs. Lubrication required by the cells or tissues to be able to function properly. Certain cells are capable to synthesize and secrete a substance for lubrication, such as saliva, hyaluronic acid, and so forth. Decreasing of lubricant often caused by atrophy or cellular dystrophy. In addition, an increase of activation of the coagulation system due to increasing of inflammation. Coagulation can be considered as part of the inflammatory system with many components that have relevance/strong interaction. Hypercoagulation may result in loss of structural integrity around the blood vessels that lead to stasis.[20]

ALTERATIONS OF CELLS AND TISSUES OF ORAL CAVITY IN ELDERLY

Inflammaging resulted in various changes of cells and the oral tissues, both hard and soft tissue. Oral soft tissue alterations due to aging include: (1) the oral mucosa. It is thinner, loses elasticity and stippling, as well as a decrease in keratin and laminin, so the mucosa increase its sensitivity to a variety of pathologic conditions such as candida infection and decrease wound healing. Furthermore, the risk of sublingual varices is increasing; (2) the mucosa of the tongue. It is smoother caused by loss of papillae filiformis; (3) cels of the gingival epithelium. It is become thinner accompanied by a decrease in keratinization; the increase in permeability to bacterial antigens; a decrease in resistance to trauma; flattening of rete pegs and cells density; (4) the gingival connective tissue. It is become rough and solid, dissolved collagen converted into insoluble collagen, thereby increasing the mechanical strength. It is reported at least there are 17 genes involved in various apoptotic pathways, which related to the health of the gingival tissues in elderly patients, such as IL-1α, ABP1, IKBKB, RELA, BIRC3, BCL2A1, PIK3CG, PRKACB, PRKAR2B, CASP10, BCL2L1, BIRC3, DFFA, BCL2L1, and IAP. The gene effects were predicted to alter apoptosis receptor levels, extrinsic apoptotic pathways through caspases, cytokine effects on apoptotic events, Ca^{+2}-induced death signaling, cell cycle checkpoints, and potential effects of survival factors; [27] (5) the periodontal ligament tissue. A decrease in the number of fibroblasts with more irregular structures, the production of organic matrix and epithelial cell rests decreasing, and an increasing number of elastic fiber, the width of the periodontal ligament is also altering, and pockets deepen. These conditions should be anticipated in order to avoid tooth loss; (6) the salivary glands and rate of salivary secretion decrease: atrophy of acinar tissue, proliferation of gland duct element, degenerative changes in the minor and major salivary glands; and decreased salivary secretion. [29-33]

Some alterations due to hard tissues imflammaging, include: (1) cementum: an increase of mineral deposition, so that the thickness increases, especially in the apical and lingual; an increase of content of fluoride resulting in lower permeability and capacity of remodeling and an increase in surface irregularities due to resorption; (2) alveolar bone: an increase in resorption, a decreased osteogenic potential, the slower of healing process; (3) teeth: attrition, shape enamel changed, thicker dentin with the formation of secondary dentine resulting in the closure of tubules dentin (sclerotic dentin), teeth pulp has more fiber and the lesser

cells and a decrease in the volume of pulp, discoloration, calcification of the pulp; and (3) temporomandibular joint tissue on the elderly people showed degeneration of cartilage due to damage to proteolytic macromolecules, matrix metallo-proteases (MMPS), which induces an inflammatory reaction in the synovial membrane, an increased local synthesis of proteases and pro-inflammatory cytokines, such as interleukin-1β-converting enzyme/ICE, interleukin/IL; membrane-type matrix metalloproteases/ MT-MMP; tissue inhibitor of matrix metalloproteases/ TIMP; urokinase plasminogen activator/u-PA, which serves to stimulate temporo mandibular joint damage stimulation.[29-33]

DISCUSSION

Not all age-related disease of the elderly caused by chronic inflammation. However, many are stimulated by a low level of chronic inflammation, persistent, systemic, and pro-gressive. Inflammaging, generally leads to retrogressive, progressive and adaptation of cells and tissues. These alterations can be very significant risk factor for morbidity and mortality of the elderly people.[1,6,33]

Inflammaging process requires several cytokines, molecular pathway, effector cells, and tissues response, to be able to generate a disease. Alterations in intracellular signaling and transcriptional pathways that regulate inflammaging influenced by many factors, so it requires a wider research to identify the cause of the disease. This research is including the regulation at the level of transcription and translation, the regulation by micro-RNA, as well as post-translational modification.[4,8,10]

The relative effective strength and anti-inflammatory response is important to overcome or compensate alterations in the inflammaging process. The production of local pro-inflammatory cytokines proven to encourage changes in phenotype and age associated pathology. IL-6 is a powerful component of chronic inflammatory that associated with age-related disease. IL-6 is now a common marker on inflammmaging. Other inflammatory mediators that increase in some age-related disease is IL-1β, IL-6, IL-8, IL-18, TNF-α, and CRP. All of the cytokines have pleiotropic effects and stimulate an immune response. [10,24]

In addition, several factors reported also cause inflammaging response in the elderly, such as genetic variants, foods, environments and body weight. Genetic variants probably reduce the sensitivity and the capacity of an inflammatory response, and enhance the anti-inflammatory response. This situation will accelerate the aging process. So, identification of pathways that controls age-associated inflammaging link with several age-related diseases is needed to explore, in order to inflammaging can be controlled adequately.[3,7,8]

Interventions that suppress, prevent, or change the dynamics of inflammaging may treat or prevent age-related disease. Moreover, genetic variants, foods, environments and body weight as a reservoir for inflammaging reaction must be control efficiently. If the quality of the oral environment improves, it may inhibit inflammaging link with age-related disease. Dentist need to distinguish between the aging process and general disease process carefully. Signs of aging in the oral mucosa and underlying microscopic changes need to be known precisely, including damage repair mechanisms of the oral tissues. In order to obtain the proper dental care for elderly.

CONCLUSION

1. Inflammaging is an important risk factor causing damage/tissue degeneration, which is very significant to cause morbidity and mortality in the elderly.
2. Inflammaging with inflammation from the disease shows different characteristics. Therefore, examination of the signs of aging on the oral mucosa needs to be done carefully so as dental treatment can be determined precisely.
3. A healthy lifestyle and diet, as well as physical exercise is allegedly to contribute in reducing inflammaging and age associated pathological processes.

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