Secret of aging and Progeria

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Abstract

Aging are both global and domestic issues. In Korea, the population aged 65 and over accounted for 14.8% of the total population in 2018 and 14.4% in Jeju island. The Korea National Statistical Office estimates it will reach 41% by 2060. As the elderly population increases, socioeconomic policy changes and researches on health aging have been carried out especially in developed countries. Representative studies are telomere studies and molecular inflammation. Korean researchers also have made efforts to elucidate the secret of aging including TLR5 (Toll-like receptor 5)/caveolin study in Jeolla province, and ROS (reactive oxygen species) and molecular inflammation in Gyungsang province. However, Research on aging is still underway and research on gut microbiota started in Jeju province, centering on progeria, is expected to give hope.

Key words :
secret, aging, progeria, in Jeju island , the elderly population increases, socioeconomic policy changes, researches on health aging

Introduction

The Hippocratic Corpus proposed that the ageing process resulted from the gradual and progressive loss of heat from the body[1].Though aging was a topic from the Hippocrates, the proportion of people over 65 years of age, both globally and nationally, in the total population is increasing and it is a socially and economically burdensome subject and it became an important research topic[2]. Although there are many people who are dependent on everyday life because of their age, cerebral cardiovascular disease and dementia, studies on centenarian or near-centenarian have shown that this tendency can vary from effort to work[3].They were able to maintain their personal lives without having to depend on others and to work even when they were older, and they had a different diet and exercise habits than older people who did not[4].

Animal research on aging is traced back to 1930's. McCay at Cornell university reported that rats fed with diets restricted in calories showed smaller sizes but extended lifespan than rats with normal diets[5]. McKay has not made further progress since the results of the experiment did not match the hypothesis and common theory at that time that lifespan and body were proportional. UW-Madison team reported similar findings in monkeys that calorie restricted diets gave benefits in lifespan and decrease in cancer, cardiovascular disease, and insulin resistance[6]. However, NIA (National institute on aging) team showed that no significant increase in lifespan but a trend for a delay in age-associated disease onset and suggested that the effects of calorie restriction in a long-lived animals were complex and likely dependent on various factors of environment, nutrition, and genetics[7]. Since then, many studies have turned to a more realistic theme, health longevity and paid attention to 'life without illness' and tried to approach from the level of various diseases accompanying it.

Global aging research

The Nobel Prize was awarded in 2009 to Elizabeth H. Blackburn in USA for the discovery telomeres[8], and the telomere length was expected to be related to the extension of the life span and attracted much attention. However Niajou, et al at University of California found that TL (telomere length) may not be a strong biomarker of survival in older individuals, but it may be an informative biomarker of healthy aging. Associations were evaluated using Cox proportional hazard models and linear regression analyses where appropriate. TL (in kilo base pairs) was not associated with overall survival (hazard ratio 1.0; 95% confidence interval 0.9–1.1) or death from any specific underlying cause including infectious diseases, cancer, or cardiac and cerebrovascular diseases. TL, however, was positively associated with more years of healthy life (beta = 0.08 +/- 0.04, p = .03)[9].

Another family of proteins that have been implicated in aging are the sirtuins, which are highly conserved enzyme homologues of the yeast Sir2 proteindiscovered in USA in 1987 [10]. Although in 1999 Kaeberlein, et al showed that deletion of Sir2 shortens yeast lifespan and that Sir2 overexpression extends yeast lifespan, there is still much debates regarding true nature of sirtuins and their connection to longevity[11]. However, it is clear that mammalian sirtuins, are critical to a healthy life[12].

Other markers includes TXNIP and Klotho genes. TXNIP (thioredoxin-interacting protein (TXNIP), also known as Vitamin-D_3-Upregulated-Protein 1 (VDUP1), is a negative regulator of thioredoxin-1 (TRX) which is a crucial role player to respond to oxidative stress[13]. Recently Oberacker, et al in Germany showed that experimental overexpression of TXNIP in flies shortens lifespan due to elevated oxidative DNA damage, whereas downregulation of TXNIP enhances oxidative stress resistance and extends lifespan[14]. Studies with extended life spans have not been done, but TXNIP is an expected marker of aging.

In 1997, Japanese researchers reported a new gene, klotho named after a Greek goddess Klotho who spun the thread of life. It induced complex phenotypes resembling human premature aging syndromes when disrupted [15]. Since then, various functional aspects of the klotho gene have been investigatedand phosphate retention associated with Klotho deficiency was universally observed in patients with CKD, suggesting that CKD might be viewed as a state of accelerated aging [16].

Domestic aging research

Yamada from USA first coined the term caveolae intracellulare in 1955 to describe conspicuous, 50–100 nm invaginations of the plasma membrane found in gallbladder epithelial cells[17]. In 1992, Rothberg, et al named caveolin which serves as the primary structural component of caveolae[18]. Park et al, in USA reported that provide the first demonstration that loss of Cav–1 gene expression and caveolae organelles dramatically affects the long–term survival of an organism in 2003[19]. Cho, et al in Korea also suggested prime modulator molecules, represented by caveolin–1, play a key role in determining the senescent phenotype, either as a physiological response or altered morphology in 2005[20]. She also reviewed in 2017 that Cav–1 up–regulation had a vital role in maintaining and stabilizing TLR5 against immunosenescence contributing to understanding of innate immunity in aging and the need to extend Cav–1 research in immunity[21].

In 1956, Harman in USA suggested the free radical theory that aging and the degenerative diseases associated with it were attributed basically to the deleterious side attacks of free radicals on cell constituents and on the connective tissues[22]. The free radical theory was succeeded and developed to ROS (reactive oxygen species) theory In 1994 by Korean researcher Yu BP in USA[23]. This ROS theory was one more time succeeded and developed to molecular inflammation theory in 2009 by Korean researcher Chung HY in Korea. He reviews that accumulated data strongly suggested that chronic upregulation of pro–inflammatory mediators (e.g., TNF–alpha, IL–1beta, IL–6, COX–2, iNOS) are induced during the aging process due to an age–related redox imbalance that activates many pro–inflammatory signaling pathways, including the NF–kappa B signaling pathway. These pro–inflammatory molecular events plays their role as basic mechanisms underlying aging and age–related diseases[24].

Aging research in Jeju island

Jeju development institute is trying to develop policy action plans that Jeju Island needs to promote consistently to join the World Health Organization Global Network of Age–Friendly Cities and Communities[25]. Cheju Halla Hospital recently conducted anti–age related disease project with low sugar diet[26] and exercise and has done research on aging with emphasis on progeria and gut microbiota. Progeria is an accelerated aging disease typically caused by a de novo mutation leading to autosomal dominant single base substitution in the Lamin A gene. In a recent research study, Aliper et al in USA showed that progeria is comparable to normal aging with respect to cellular signaling pathways, and that progeria truly recapitulates the normal aging process[27].

Nobel laureate Elie Metchnikoff hypothesized that age–related illnesses are primarily the consequences of reactive phagocytes impairing healthy tissues as a response to autotoxins in the gut, and that restoring gut microflora by regularly ingesting yogurt could promote healthier aging. The human gut microbiome keeps on fluctuating and undergoes the most prominent deviations during infancy and old age. The concept of interventioning gut microbiota for healthy aging can be promising option to aging[28]. Cheju Halla general hospital is establishing the Asia Progeria Foundation together with Wonki who is the only progerian in Korea[29]. It is conducting research of feces from the progerians in Colombia and Philippines.

Conclusion

Aging research, which started in earnest in the mid–1900s, has undergone a trial–and–error process so that in recent years it can understand the process of aging and prevents the aged from being linked to disease or senility. In other words, gerontology is a study of how to live a healthy lifetime, a variety of studies are being conducted both domestically and internationally, but a field study of children with progeria with emphasis on gut microbiota at the Cheju Halla Hospital is expected to meet this goal.

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