Introduction

Mechanisms of aging, age-associated diseases, and lifespan determination

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There are three types of research investigating the mechanism of aging. The first one investigates the mechanism of age-dependent changes in the cells and tissues controlling the timing of the onset of age-associated disease. The second one investigates the mechanism of lifespan determination. The third one investigates the mechanism of age-associated diseases (e.g. Alzheimer's disease, age-associated macular degeneration, sarcopenia, cancer, and others). The fourth one investigates the interventions extending the lifespan. The interventions are usually developed as a result of understanding the mechanism. Therefore, the intervention studies may be included in the other three types as the method to prove the proposed theories. In this thematic issue, there are eight articles covering all these four types of aging research. The brief background and the summary of each article are described below.

Mechanism of age-dependent changes

The first two minireviews cover the recent progress of the understanding of aging at the level of DNA methylation. It has been known that there is an age-dependent change of DNA methylation, especially in blood cells (reviewed in Bell *et al.*¹). In 2013, Steve Horvath² reported that DNA methylation of the specific 353 CpGs could be used to predict the age of the cells from different types of tissues of the human body. In 2018, Steve Horvath reported the improved version of the age-predicting method using 391 CpGs, which can be used to study the epigenetic aging of the cultured human cells, including fibroblasts.³ The new version of the age estimator is considered as the most accurate age estimator at present that predicts the age of the cell and the tissue.⁴ The estimated age by DNA methylation analysis is called DNAmAge.^{2,3} The first minireview by Raj and Horvath⁵ overviews the recent progress of the understanding of the mechanism of DNAm age progression. This article explains the history and the background of the discovery of Horvath's multi-tissue age estimators, and the authors concisely overview the most up-to-date

understanding of the significance and the mechanism of epigenetic aging. The second minireview by Matsuyama *et al.*⁶ also covers the recent progress of the studies of epigenetic aging by focusing on their recently published articles. The minireview by Matsuyama *et al.* reports the in-depth discussion of the cell-intrinsic epigenetic aging mechanism of blood cells,⁷ the effects of environmental oxygen on the epigenetic aging,⁸ and the role of tumor suppressors in the epigenetic aging.⁸

Lifespan determination mechanism

Nematode (*C. elegans*) is an ideal tool to investigate the mechanism of lifespan determination because of the short lifespan and the powerful genetics. However, the mechanism of aging of vertebrate and invertebrate may not be the same. For example, the majority of the cells in the matured nematode do not divide after the maturation, whereas the human body is maintained by the turnover of the old and new cells. If the death of the long-lived essential cells determines the timing of the lifespan termination, it means that the lifespan of the particular cells determines the lifespan of the individual organism. If this is the evolutionarily conserved mechanism of the lifespan determination, the nematode may be the best tool to reveal the mechanism. In this issue, Chin *et al.*⁹ report their findings of the mechanism of aging using the nematode model. The authors focused on the age-dependent decline of motor activity. Very importantly, authors discovered that arecoline, a muscarinic acetylcholine receptor agonist,¹⁰ is effective in preventing the age-dependent decline of the motor activity and extending the lifespan in the *C. elegans* model. These findings will advance the development of interventions slowing down the age-dependent decline of muscle strength, such as sarcopenia.

Mechanism of age-associated diseases

The next five articles cover the research fields studying the mechanism of age-associated diseases. Cell senescence is

considered one of the causes of age-associated degenerative diseases.¹¹ Senescent cells secrete a group of inflammatory cytokines inducing chronic local inflammatory reactions.¹¹ This character of senescent cells is called senescence-associated secretory phenotype (SASP).¹¹ Based on this concept, one of the popular research fields is the development of senolytic drugs inducing apoptosis of senescent cells.^{12,13} Chandrasekaran *et al.*¹⁴ report the novel mechanism controlling SASP of senescent cells. The authors focused on the role of Ca^{2+} homeostasis in the cell. They discovered that H_2O_2 -dependent Ca^{2+} entry through plasma lamellar channel is weakened in the senescent cells. This discovery allowed the team to uncover the previously unknown roles of redox and the mTOR-mediated reaction of the cells controlling SASP through Ca^{2+} homeostasis. Their findings may contribute to the development of the therapeutics suppressing SASP of senescent cells.

Mitochondria produce energy, but they also generate reactive oxygen species (ROS) inducing damages to the cellular components (DNA, protein, lipids, and others). Therefore, the dysfunction of mitochondria impacts on the health condition affecting the lifespan. In this issue, two articles cover the role of mitochondria in aging. Previously, Ikeda's laboratory discovered that transmembrane protein 135 (Tmem135) regulates mitochondrial dynamics (fission and fusion), and the dysfunction of Tmem135 is linked with age-associated vision loss in mice.¹⁵ The mechanism of how Tmem135 regulates mitochondrial dynamics is not yet well understood. In this issue, Lee *et al.*¹⁶ report their discoveries of the effects of Tmem135 on the metabolisms in the hippocampus, cerebellum, heart, and retina in the mice. The authors performed multiple metabolomic analyses of these tissues obtained from mice expressing both wild type and mutant Tmem135. The results showed that Tmem135 impacts the metabolisms, especially NAD^+ related physiological processes, and the degree of the impact varies depending on the tissue types.

Termsarasab *et al.*¹⁷ report the results of their analysis of the subcellular localization of transactive response DNA-binding protein 43 (TDP-43) in young and old mice. In normal healthy cells, TDP-43 is expressed in the nucleus; however, TDP-43 has been shown to localize in the cytosol and mitochondria in the degenerating neurons of age-associated diseases such as Alzheimer's disease.¹⁸ In this article, Termsarasab *et al.* determined whether the subcellular localization of TDP-43 changes during "healthy" aging without a major neurodegenerative disorder. Termsarasab *et al.* found that there are no major changes in the TDP-43 distribution in the cell between young and old "healthy" mouse brains.

The intervention of age-associated degenerative disorders

Nicotinamide adenine nucleotide (NAD) plays an essential role in numerous cellular activities as the cofactor and the substrate of various enzymes. The level of NAD is known to decrease in aged rat¹⁹ and human.²⁰ Since NAD and its homologs can be easily taken as supplements, the public

interest in NAD research became very high. In this article, Kincaid and Berger²¹ explain the history and current understanding of the significance of NAD in aging as well as cancer.

Parmer *et al.*²² report the potential benefit of retinoid analogs and polyphenols in preventing age-associated macular degeneration (AMD). Recently, the authors discovered that the flavonoids protect the vision system by stabilizing rhodopsin.²³ This rhodopsin stabilization activity of flavonoids may have a therapeutic potential to treat AMD. This minireview covers the current understanding of the health benefit of the plant-derived retinoid analogs and polyphenols by focusing on their effects on the vision system.

Conclusion

This thematic issue of "Mechanism of Aging" is the first thematic issue publishing articles related to aging research in Experimental Biology and Medicine (EBM). The current issue demonstrates that EBM is an ideal international journal that publishes cutting edge articles reporting exciting findings in the aging research fields.

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