alpha-Klotho in health and aging

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Aging is the biggest challenge that mankind has to deal with in this century. The recent achievements of aging researches created new directions; (1) delaying aging; (2) realization of the healthy longevity; and (3) suppression of dysfunctions caused by aging.

alpha-klotho was first identified as an aging gene and later shown to have several functions depending on its intracellular, membrane, and extra-cellular secreted forms. The intra-cellular form of alpha-KI activates Ca2+ transport in the choroid plexus and kidney, and regulates PTH secretion in parathyroid glands by controlling the trafficking of Na+-K+-ATPase complex to plasma membrane. On the membrane, alpha-KI forms a complex with FGF23 and FGFR1 and negatively regulates 1, 25(OH)2D synthesis and phosphate re-absorption in the kidney. The extracellular domains of alpha-KI are homologous to family 1 beta-glycosidase. The analyses of sugar chains of alpha-KI binding proteins and crystal structure of alpha-KI revealed that alpha-KI functions as a novel glucuronide-binding protein. A vicious cycle composed of abnormality of mineral homeostasis, calpain1 activation, and the increase in inflammatory cytokines and chemokines is involved in the onset and deterioration of aging related phenotypes of alpha-kI deficient mouse. Multiple aging-related phenotypes were strikingly ameliorated by the functional suppressions of vicious cycle components.

These findings allow us to propose that the modulation of vicious cycle components is a potential therapeutic option for delaying age-associated organ pathology.

Roles and mechanisms of cellular senescence in aging and cancer

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Cellular senescence is the state of essentially irreversible cell cycle arrest that can be induced by a variety of potentially oncogenic stimuli, such as telomere erosion, oxidative stress or activation of certain oncogenes and is therefore considered to act as an important tumor suppression mechanism. However, emerging evidence indicates that senescent cells may also promote deleterious side effects including chronic inflammation and cancer promotion. It is therefore quite possible that accumulation of senescent cells in vivo may contribute to aging-associated intractable diseases. Here, I discuss the molecular events associated with these two faces of cellular senescence, focusing on the pro-inflammatory side effects. I believe that a better understanding of the molecular mechanisms involved will lead to new strategies for the prevention of aging and aging-associated diseases.
S4-3 Epigenetic alterations in aged hematopoietic stem cells

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Hematopoietic stem cells (HSCs) show several characteristic phenotypes with aging, such as impaired repopulating capacity and a greater propensity for myeloid differentiation compared with young HSCs. Epigenetic alterations have been recognized as a hallmark of mammalian aging. This epigenetic drift is thought to be the result of the stochastic accumulation of epigenetic errors, but also induced by various aging stresses or acquired somatic mutations in epigenetic regulator genes. Although global H3K27me3 levels do not significantly change in mouse HSCs with aging, we found that Polycomb Repressive Complex (PRC) 2 target genes, which are marked with a repressive histone mark H3K27me3 in young HSCs, show a trend toward up-regulation in aged HSCs and mildly reduce H3K27me3 levels at their promoters. We confirmed some of the aging stresses induce decline in H3K27me3 levels in HSCs. These findings suggest that a decline in polycomb activity is associated with HSC aging. Of note, recurrent mutations in PRC2 genes have been identified in age-related myeloid malignancies; such as myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN), which are all clonal myeloid disorders originating from HSCs. We confirmed that the loss of Ezh2, an enzymatic component of PRC2, in mice markedly accelerates the development of age-related myeloid malignancies. These findings suggest that aged-related decline in polycomb activity underlies the development of age-related HSC malignancies.

S4-4 Stem cells orchestrate hair follicle aging program

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Tissues and organs undergo structural and functional declines due to aging, yet the underlying mechanisms involved and whether the tissue aging is programmed or not have been poorly understood. The hair follicle is a mini-organ of the skin that is specialized to grow hair. Hair follicle stem cells (HFSCs) and melanocyte stem cells (McSCs) reside in mammalian hair follicles to sustain the cyclic growth of pigmented hair during each hair cycle. To understand the mechanisms of tissue aging, we have studied the physiological aging-associated changes in murine and human hair follicles and their underlying mechanisms. In vivo fate analysis of stem cells in naturally aging hair follicles revealed that those stem cells undergo specific fate changes through the proteolysis of hemidesmosomal transmembrane collagen (COL17A1), thereby causing aberrant differentiation and depletion of those stem cells and the resultant typical hair aging phenotypes in a stepwise manner. Furthermore, we found that the expression of those aging phenotypes can be prevented by the forced expression of COL17A1 in HFSCs. These results demonstrate the existence of a stem cell-centric aging program as the core to orchestrate tissue aging. In this symposium, I will introduce the concept of stem cell division program for aging and will discuss the role in tissue/organ aging.
The Senescence-Accelerated Mouse (SAM) strains provide a unique model system for the study of the aging process in higher organisms. The SAM strains were developed in 1981 and have been used in many studies of aging, age-related diseases and anti-aging treatments. The SAM strains include the accelerated senescence-prone SAMP series (SAMP1, SAMP6, SAMP8 and SAMP10) and the accelerated senescence-resistant SAMR1 which serve as a control for the SAM strains. The SAMP strains grow normally, but they show early signs of aging and their life spans are shorter than SAMR1. Molecular genetic characterization of the SAM strains revealed that they might be a group of recombinant inbred strains involving the AKR/J strain and an unknown strain. SAMP strains spontaneously manifested various age-related patho-biological phenotypes that were often characteristic enough to differentiate the strains. The hyperoxidative status may incur accelerated senescence in SAMP strains. We have revealed delayed senescence in SAMP1 mice given supplementation with reduced form of coenzyme Q10. Activation of mitochondrial function by the reduction in cytosolic Ca\(^{2+}\), increased cAMP, induction of Sir2u genes and PGC-1 α may protect against the progression of aging and the symptoms of age-related diseases in SAMP1 mice.

The Japan Mouse Clinic (JMC) has conducted comprehensive phenotyping of every gene of KO mouse lines based on IMPReSS (International Mouse Phenotyping Resource of Standardized Screens) from 2011. We have examined young mice (up to 16 weeks old) in many lines and from 2016 we constructed late-onset pipelines for mice aged 49-57 weeks old in the IMPC ageing pipeline. Control data for the late-onset pipeline has been published for the C57BL/6NcJ mouse strain and the results are available through the JMC website (http://mouseclinic.brc.riken.jp/control-aged_mice/). We have also completed the aging pipeline for 16 knockout (KO) lines in the pipeline and in our analysis, we found that a comparison of genotypes was insufficient to determine the effect of the KO gene on aging (refer to Kozawa’s poster presentation). By the way, it is necessary to produce and supply aged mice to the scientific community for aging research. Aging is a complicated phenomenon, however, and same-aged mice can have various phenotypes as a result of breeding conditions or many other factors. Examination of factors such as breeding cage size, number of mice per cage, and enrichment (or lack thereof) has been started for C57BL/6J and C57BL/6N mice, which are thought to be representative mouse lines. We will compare these mouse phenotypes using a modified SHIRPA examination, hematology, biochemistry, and autopsy for an aging phenotype index. Finally, we will propose the optimum breeding system for breeding (producing) and maintaining aged mouse.