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Chapter 6

Antiaging — Effect of Stem Cells on Aging and Stem Cell Aging

Jisook Moon and Sang-Hun Bae

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Abstract

Aging is defined broadly as the normal progressive process, consequently leading to growing vulnerability to disease and death. A major challenge lies in dissecting the underlying mechanisms of aging with conventional experiments due to the complexity of and multicontributions to the aging process, reflecting a need for investigation into it in various aspects. For this reason, the age process has currently been subjected to OMICS technologies including genomics, transcriptomics, proteomics, and metabolomics, allowing the exploration of age-related changes in a multifactorial manner. In addition, since age-dependent decline in stem cell function is almost identical to the biological age, stem cells have used to understand "aging" and to investigate key reverse factors for "antiaging". This suggests that a range of new approaches are needed to reveal the unknown biological basis for aging at a variety of different molecular levels using stem cells as a tool of normal aging process and can further apply fundamental aspects in biological aging and longevity.

Keywords: Aging, OMICS, Stem Cells, Transcriptoms, Longevity

1. Introduction

Aging is defined broadly as the normal progressive process, consequently leading to growing vulnerability to disease and death. The fact that the aging process is inevitable yet controllable has made it attractive for the research focusing on age-associated molecular changes. A major challenge lies in dissecting the underlying mechanisms of aging with conventional experi-

ments due to the complexity of and multicontributions to the aging process, reflecting a need for investigation into it in various aspects. For this reason, the age process has currently been subjected to OMICS technologies including genomics, transcriptomics, proteomics, and metabolomics, allowing the exploration of age-related changes in a multifactorial manner. This suggests that a range of new approaches are needed to reveal the unknown biological basis for aging at a variety of different molecular levels and can deepen our understanding of fundamental aspects in biological aging and longevity.

The aging process is characterized by gradual, cumulative damages to structure and function of stem cells which exist during the life of organisms. We will discuss here the integrative studies of the stem cell aging and a therapeutic effect of adult stem cells including the umbilical cord blood and the underlying mechanisms of the complex process at diverse molecular levels, with the final goal of practically applying stem cell treatment to the aged for maintaining health over time. In addition, an integrated method, OMICS technology that would help us understand a complex biology of aging will be discussed. Aging can be conceived of as a process that a pool of endogenous stem cells loses progressively its ability to replenish the damaged cells over age. In almost all living organisms, the time-dependent decline in regenerative potential of stem cells is responsible for an increased susceptibility to aging and several age-related diseases. The reduced regenerative capacity of endogenous stem cells has been explained partly by DNA damage, changes in stem cell niches, and activation of tumor suppressor gene. It is unclear; however, to what extent the factors contribute to human ageing, especially stem cell aging, and determine even life span. Its complexity demands new approaches for clarifying the multifactorial processes.

2. OMICS technologies and stem cell aging

Recently, to gain a deep insight into the biology of aging, new high-throughput technologies, also known as “OMICS”, are being utilized in a variety of ways to investigate the molecular changes observed during ageing ; OMICS refers to studies with suffix “-omics” designed to collectively characterize and quantify pools of molecules at different levels, including genomics, transcriptomics, proteomics, and metabolomics. A series of experiments using the OMICS have been attempted to establish any link between molecular changes and aging. However, the studies so far on aging heavily rely on blood samples which consist of different cell types and usually focus on one technology of OMICS, thereby placing obstacles in the way of interpretation on the phenomenon or bringing misinterpretation of the complex aging process. Another challenge in the study is tissue-specific changes in gene expression with increasing age, adding more complexity to understanding the process. Accordingly, an alternative approach can be to focus on stem cell aging among diverse hallmarks of the process using OMICS technology. Stem cells serve as endogenous replacements for cells lost to homeostasis and injury through adult life. The regenerative capacity deteriorates in numerous tissues with advancing age, frequently failing to meet the demands of the developing tissues and then leading to multiple ageing-related phenotypes or diseases. As a result, accumulation of damage in the function could be reflected in diverse macromolecules from DNA to metabolite,

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considered as closest to phenotypes, during aging. The damaged macromolecules in turn disrupt the pathways contributing to stem cell dysfunction during the aging process, resulting in a vicious cycle. In addition, decreased pools of tissue stem cells are likely to be associated with function declines in hematopoiesis, neurogenesis, and myogenesis during aging, suggesting that a key to reverse or delay the aging process resides in deepening our understanding of the adult stem cells. As with other factors for aging, the mechanisms that induce the time-dependent stem cell decline still remain elusive and thereby need to be evaluated in an integrative manner for which OMICS technologies may be appropriate. Understanding the molecular processes involved in stem cell dysfunction may shed light on the causes of aging, eventually employing therapeutic strategies that reverse the decline process. Maintenance of stem cell pools or stem cell rejuvenation holds great therapeutic promise for age-related impairments. For example, heterochronic parabiosis, such as the shared circulatory or physiological system between the young and aged, has been reported to be effective in reversing age-related phenotypes by improving stem cell function. One representative study on the parabiosis showed that the supply of young blood to aged mice ameliorates cognitive impairments by enhancing synaptic plasticity in the brain. Another experiment demonstrated that when exposed to the niche of young mice's muscles, aged mice regenerate impaired satellite cells to restore muscle regenerative potential. Emerging evidence also indicates that reduced regenerative capacity is reversible and that the aging process can be postponed by improving stem cell function to replenish the damaged tissues. This raises the possibility that treatment of stem cells from diverse origins may reengineer the aging-related defects by replacing aberrant stem cells in the aged tissue. With widening applications, metabolomics today is surfacing as a new approach to decipher the regulation of metabolism involved in aging. Metabolites are end products of complex biological events and can be considered as ultimate responses to internal states or external forces, probably providing unrepresented insights into how stem cell declines influence human aging. Oxidative metabolism and the maintenance of mitochondria have been shown to be associated with stem cell aging. Consistently, metabolic states in stem cells play a crucial role in determining whether the cells are bound for proliferation or differentiation; both cell states are mainly associated with mechanisms controlling the balance between glycolysis and oxidative phosphorylation. In addition, clinical studies on aging with metabolic profiles showed the age-specific metabolites having strong correlations, some of which are associated with fatty acid oxidation, underscoring the role of metabolomics in the interpretation of the aging process.

2.1. Transcriptome analysis of neural stem cells during dopamine differentiation

Accordingly, first of all, our study investigated gene expression changes of neural stem cells during differentiation into dopaminergic cells and with increasing passages in a proliferation state, both of which can be seen as aging: differentiation as a part of "chronological aging" and increasing passage as "replicative aging". Neural stem cells showed cell stage-specific patterns of gene expression during differentiation and specific genes participated in neurogenesis by forming a molecular co-expression network. When sustaining a proliferation state, the stem cells induced the expression of genes whose products are involved in phosphorylation, cell proliferation, kinase cascade, response to stress, and signal transduction. As entering into a

differentiation stage, the up-regulated genes are mostly related to mitotic cell cycle, mitosis and cell division. At a late differentiation stage, genes for synaptic transmission and regulation of synaptic plasticity were expressed at higher levels. The results clearly showed that as cells age from proliferation to differentiation, different biological processes are involved in stem cell aging, probably generating metabolites unique to cell states.

2.2. Transcriptome analysis of hypoxic effects on placenta-derived cells with increasing passages

Also, we determined the effects of hypoxia or normoxia on the placenta-derived cells with increasing passage based on the transcriptome data. In gene ontology analysis, most genes significantly upregulated under hypoxia were associated with cell proliferation, macromolecule synthesis, metabolic pathway, signaling pathways, and cellular homeostasis, as confirmed by the in vitro result that the hypoxic culture condition enhanced the proliferation capacity. Downregulated genes were enriched for cell death/apoptosis and protein aggregation, supporting the notion that protein homeostasis and balance between proliferation and quiescence are crucial to stem cell aging. These results suggest that under hypoxia the stem cells experience enhanced proliferation and survival, inhibiting cell death and pro-aging pathways. At a late stage, genes that are differentially expressed under hypoxia are enriched for nucleosome assembly and chromatin organization, suggesting the involvement in epigenetic regulation. Lastly, we carried out metabolite profiles in aged mice transplanted with placenta-derived cells. Most of increased metabolites by cell treatment were related to lipid metabolites, which is likely to be associated with unique patterns of gene expression after cell transplantation, encouraging further studies of integrating OMICS data. These findings add weight to the notion that the study of stem cell aging with OMICS is an efficient means for elucidating the biological basis of the aging process. In line with these findings, an effect of human umbilical cord blood infusion, youngest blood we can obtained, on old mice (more than 23 months old) has been investigated in our laboratories, and a human clinical trial using human umbilical cord blood infusion into old subjects is underway. In addition, human placenta-derived MSCs (hpMSCs) have been used as a candidate for antiaging treatment. Our animal studies exhibited better cognitive functions measured 12 weeks after hpMSCs injection. For further translational studies, analyses using OMICS technology is ongoing.

3. Conclusions

Complex physiological changes and individual differences in aging have always challenged the efforts of scientists to understand the normal process, which demands new strategies capable of studying molecular changes in an integrative manner rather than traditional experimental approaches. Through OMICS technologies, it is possible to measure dynamic molecular changes simultaneously at diverse levels with the generation of high-throughput data in different types, consequently facilitating the identification of aging/antiaging biomarkers and thereby preventing age-related diseases. The studies of OMICS have provided novel insights into what molecular pathways determine the progressive and complicated process, although much needs to be clarified. In particular, metabolite profile can propose unprece-

dented notions of ageing when combined with genomics, transcriptomics, and proteomics. Taken together, the integration and context-dependent interpretation of multidimensional OMICS data is helpful in understanding the complex process of aging.

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