Bae et al. Biomedical Dermatology (2017) 1:9
DOI 10.1186/s41702-017-0007-2

Biomedical Dermatology

REVIEW Open Access

Perspectives of aging study on stem cell

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Abstract

Aging is the result of a complex polygenetic trait characterized by decreased regeneration capacity and increased vulnerability to external and internal perturbations. Consequently, the inevitable process critically influences longevity, health, and disease susceptibility, ultimately leading to age-related pathologies and death. Gaining insights into inherent properties of aging and identifying definitive biomarkers and/or signatures are prerequisites for a better understanding and for the design of therapeutics for a wide range of age-related diseases that would improve the quality of life of the elderlies. However, a comprehensive understanding of the molecular mechanisms underlying aging has been hampered by its complex nature. Although the process has been subjected to substantial data-driven analyses including genomics, transcriptomics, and proteomics in a systemic manner, aging's complexity hampers proper analysis as well as interpretation of the resulting outputs. Therefore, we review recent consequences focused on stem cell aging and age-related diseases.

Keywords: Aging, Stem cell, OMICS technology, Target therapy

Background

Multicellular organisms experience a gradual loss of repair potential and tissue homeostasis with age, consequently resulting in age-related decline in organ function and intractable age-related diseases. The progressive deterioration in regenerative potential with age is closely linked to a time-dependent decrease in functionality of tissue-specific stem cells including endogenous stem cell exhaustion, aberrant changes in the supporting niches, and functional attrition. Thus, aging can be defined as a process involving the progressive inability of tissue-resident stem cells to replace damaged cells with age, which stresses the need for more complete analyses of stem cell aging in an age-dependent context. The analysis of aged stem cells leverages rapid advancements in the field including the identification of various cell types clearly defined in terms of lineage progression facilitating their characterization in the context of aging. Based on the conceptual framework of stem cell aging, the analysis of aged stem cells has been recently postulated to be one of the more promising approaches to decipher the fundamental aspects of aging. However, the significant challenge remaining is a better translation of our knowledge of aged stem cells to the general process of aging (Jones and Rando 2011). Here, we discuss recent findings on stem cell aging and ask whether clinical manipulation of stem cells in particular or multiple tissues reverses or counteracts age-related pathological changes. These novel approaches may lead to new biological themes of the stem cell aging, which can be generalized to studies of the general aging process and potential identification of the underlying molecular pathways and therapeutic targets.

Investigation of stem cell aging provides new insights into understanding aging

Complex biological systems are designed to be robust against internal and external challenges to maintain the homeostasis of their functions (Kitano 2004). Aging process seriously compromises this fundamental feature and leaves aged organisms highly susceptible to lesser/minimal changes and damages, as manifested by a reduced capacity of resident stem cells to replenish cells lost to age-related pathological changes (Oh et al. 2014). Stem cell exhaustion with age is consistently observed in diverse tissue-specific stem cells including muscle (Cerletti et al. 2008), hematopoietic (Kollman et al. 2001), and neural stem cells (Enwere et al. 2004), necessitating

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studies for a comprehensive understanding of aged stem cells associated with the progressive regenerative deterioration. A parabiosis study showed that when exposed to the niche of young mice's muscles, aged mice are able to ameliorate the age-related cognitive impairments, suggesting therapeutic potential for enhancing or replacing aged stem cells and significance of stem cell aging study (Villeda et al. 2014). Many molecular processes implicated in stem cell aging are evolutionarily conserved such as the accumulation of damaged macromolecules, DNA damage, reactive oxygen species (ROS) production, TOR, and WNT signaling (Jones and Rando 2011; Oh et al. 2014). To facilitate the clinical translation of knowledge acquired from the study of aged stem cells to the process of aging, an exploration of the overlapping or conserved processes between aging and stem cells would yield interesting leads. Therefore, a comprehensive understanding of the molecular mechanisms regulating stem cell aging and their surrounding niches will provide a valuable clue for developing therapeutic strategies to delay or reverse age-related diseases. Hereafter, we will focus on the important molecular processes regulating stem cell aging before discussing the integration of OMICS technology with stem cell aging research.

Biological process underlying stem cell aging

As organisms age, somatic stem cells progressively lose their competence to deal with a battery of cell-intrinsic and cell-extrinsic challenges, which is mainly attributed to a decline in stem cell functionality. Tissue-resident stem cells frequently encounter accumulated toxic molecules generated by normal metabolism and environmental interventions, but to ensure the maintenance of cellular function, the cells must adopt appropriate strategies to respond to the damage accumulation. Among many risk drivers for the accumulation, ROS have been implicated as disrupting stem cell function and fate decision, implying that redox status in the cells may determine in part their regenerative potential (Pervaiz et al. 2009). In support of this notion, a study on the conditional ablation of Foxo family, playing a crucial role in dealing with oxidative environments, displayed that deregulation of ROS levels in hematopoietic stem cells leads to aberrant proliferation and impaired self-renewal ability (Tothova et al. 2007). Moreover, in antioxidant enzyme deficient mice, hematopoietic systems are particularly vulnerable to oxidative stress (Melov et al. 1999). Several studies suggest that regulation of toxic molecules by antioxidant agents hold great therapeutic promise for age-related pathologies (Drowley et al. 2010; Ito et al. 2006). However, studies of ROS in terms of stem cell aging require cautious interpretation, given that ROS has pleiotropic activity and exhibits the effects in a context-dependent manner (Finkel 2011). For example, an experiment on unexpected roles of ROS using neural stem cells (NSC) suggests that high levels of ROS enhance self-renewal and neurogenesis of neural stem cells in a proliferative state through PI3K pathway signaling (Le Belle et al. 2011). In the case of hematopoietic stem cells, a choice between quiescence and proliferation is likely to be determined by the extent of ROS levels (Owusu-Ansah and Banerjee 2009). With so much conflicting evidence, there is a clear consensus that when reaching a certain threshold, ROS significantly impair cellular architectures enough to induce cellular dysfunction (Hekimi et al. 2011).

The ROS theory can relate mitochondrial dysfunction to stem cell aging, although many other risk factors contribute to the functional decline in the organelle. Respiratory chain system in mitochondria becomes less efficient at generating ATP with age, resulting in elevated levels of ROS which in turn deteriorate mitochondrial genomic integrity in a vicious cycle manner (Harman 1965). Mitochondrial DNA mutations in somatic stem cells lead to impaired neural and hematopoietic progenitor, contributing to progeroid symptoms which can be reversible by altering redox states (Ahlqvist et al. 2012). Taken together, maintaining a balanced regulation of redox state in cellular compartments can have potential therapeutic values for age-induced phenotypes.

Due to a relatively frequent transition from quiescence to proliferation or vice versa, mainly in a quiescent state, tissue-resident stem cells persisting throughout life are continuously exposed to genetoxic challenges, jeopardizing genetic stability (Oh et al. 2014). As a result, it has been suggested that accumulation of genetic damage with age is a principal mechanism underlying aging stem cells by which the aged cells reduce the capacity to maintain homeostasis and fail to return to a more youthful state. Several experimental interventions which disrupt the pathways involved in DNA damage response have suggested that reduced regenerative potential with age is largely attributed to genomic instability induced by accumulation of DNA damage in stem cells (Rübe et al. 2011; Ito et al. 2004; Rossi et al. 2007). Similar to ROS, DNA damage can be transient as part of normal processes (Larsen et al. 2010) and reversed (Beerman et al. 2014) such that context-dependent interpretation must be needed in associating the damage with stem cell aging. During aging, toxic molecules ranging from damaged DNA to metabolites inevitably accumulate in multiple tissues, ultimately leading to death, suggesting that developing ways to minimize or attenuate the unavoidable phenomenon can be an efficient therapeutic avenue for age-related diseases.

Calorie restriction (CR) is considered one of the dietary interventions that can delay or reduce age-dependent pathologies (Mair and Dillin 2008). A mouse model of

young vs. aged mice revealed that short-term CR improved functionality of muscle stem cells, through enhanced mitochondrial function and metabolic benefits (Cerletti et al. 2012). In *Drosophila*, CR counteracts an age-dependent decrease in germline stem cells and extends lifespan, implying that dietary intervention can reverse the decline of adult stem cells (Mair et al. 2010). Moreover, CR enhances brain plasticity in adult rats by increasing neurogenesis and influencing production of neurotrophic factors (Lee et al. 2000). These effects have been reported to act through mTOR signaling, a converging pathway sensing and integrating intracellular and extracellular cues, deregulation of which leads to a number of pathological conditions including neurodegenerative disease, cancer, and metabolic disease (Laplante and Sabatini 2012). Accordingly, it is reasonable to propose that reducing activity of mTOR signaling could attenuate as age-dependent decline in stem cell functionality, although little is known about beneficial effects of the intervention on aged stem cells. The hypothesis is supported by the observation that age-related impairments in hematopoietic system are reversed by suppressing mTOR activity with increased life span, implicating manipulation of mTOR signaling as therapeutic potential for disrupted hematopoiesis of the elderly (Chen et al. 2009). Further studies are needed to point toward a direct link between reduced mTOR signaling and aging stem cells rescue.

Tissue homeostasis requires maintenance of a stem cell pool by fine-tuning cellular states balance between self-renewal and differentiation. The fate control rate determines the population size of a stem cell pool. A series of studies have underscored the roles of metabolic pathways in stem cell transition and homeostasis, highlighting the importance of bioenergetics in stem cells biology (Ito et al. 2004; Gan et al. 2010). Stem cells in multiple tissues are mainly in a quiescent state for prolonged periods preferring glycolysis to mitochondrial oxidative phosphorylation to generate ATP (Ito and Suda 2014). An untargeted metabolomics study of human-induced pluripotent stem cells (iPSCs) showed that somatic cells are reprogrammed into iPSCs by a transition toward a glycolytic state (Panopoulos et al. 2012). Interestingly, many metabolic properties of cancer cells are shared with those of stem cells such as TCA cycle and Gln metabolism, suggesting that a fundamental similarity exists even at the metabolic level between the two cell types (Ito and Suda 2014). Recent research into aging has extensively characterized individual variations in human blood metabolites, some of which are clearly relevant to elderly subjects, implying that metabolites can serve as an important source of information with which to explore the aging process (Chaleckis et al. 2016). Even though comprehensive metabolic profiling of stem cell aging is still lacking, rapid advances in metabolomics will provide new mechanical insights into metabolic characteristics in age-related dysfunction in regenerative potential.

OMICS technology and future study of stem cell aging

The process of aging broadly and progressively influences biological components ranging from micromolecules to cellular structures to organ systems. The time-dependent impact and complexity of the process require a novel study approach. Conventional aging research strategies accounting only for a few features of aging have been replaced by OMICS technologies, which are designed to collectively characterize and quantify pools of molecules at different levels including genomics, proteomics, and metabolomics (Sondheimer et al. 2011; Hannum et al. 2013). The massive amount of data-driven analysis could allow for exploration of age-related molecular changes in a multifactorial manner. Increased number of manually curated databases of aging in the public domain may accelerate biological data-centered studies (Craig et al. 2015; Tacutu et al. 2013). However, most OMICS studies have focused on one technology, limiting biological meaningful interpretations of the complex property, although the different OMICS data are strongly inter-correlated (Zierer et al. 2015). Moreover, many aging OMICS studies are restricted to blood analysis due to its easier accessibility, although the aging process exerts its detrimental effects across multiple tissues (Valdes et al. 2013). Despite rapid advances in OMICS technologies, a conspicuous lack of integrative methods for different OMICS data and the complexity of the aging process hinder a more system-level understanding of aging. Nonetheless, systems biology has provided a rich collection of integrative methods to overcome the obstacles, and one of the efficient methods is the integration of OMICS profiling with network approaches where molecular components such as genes or gene products are represented as nodes and mutual dependencies between them as edges (Fig. 1) (Zierer et al. 2015). Research on neurodegenerative diseases successfully adopted the integrative strategy while leveraging the availability of high-throughput neurobiology data to gain a better understanding of the complex nature of these diseases (Parikshak et al. 2015). Intriguingly, a series of studies revealed that a hierarchical structure is embedded in many biological networks including multiple molecular levels, indicating that molecular components of aging also can be modeled as networks to identify main drivers of aging. As discussed above, one of the greatest challenges lies in inferring causal links between aging and dynamic molecular changes mainly due to the inherent nature of the aging process and the lack of current biological knowledge about the progressive decline process. Accordingly, studies on stem cell aging must be carried out with

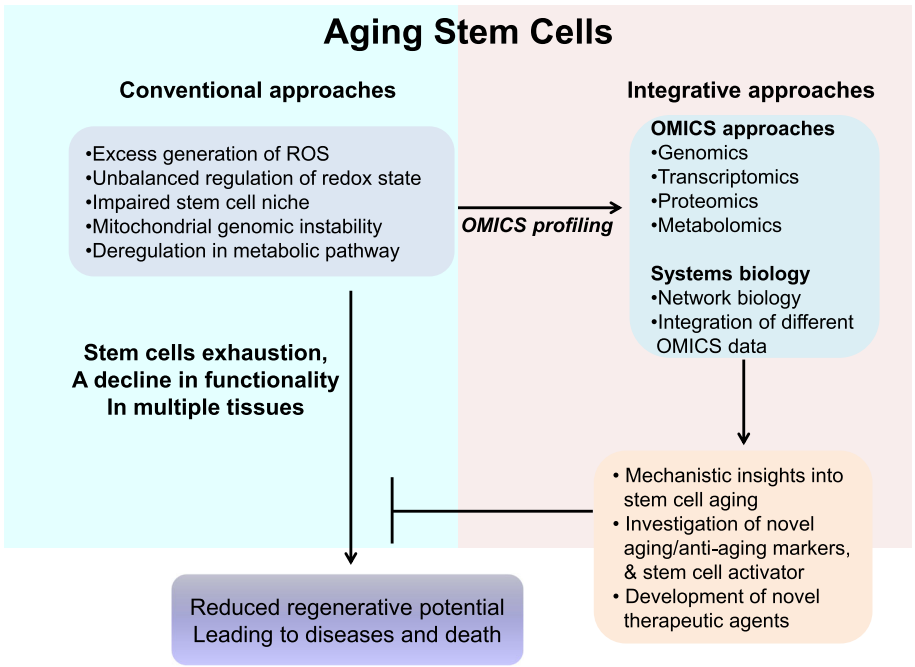

Fig. 1 Perspectives of aging study on stem cell. The integration of OMICS profiling via collaborating systems biology and OMICS approaches facilitates providing new insight and ingenious research on stem cell aging study which overcomes limits of previous OMICS data

rigorous data-driven analysis and integrative approaches to be a step beyond understanding one feature of the process at a time (Moon and Bae 2015). We strongly suggest that clarifying the fundamental aspects of stem cell aging with OMICS technologies and combining them with integrated analyses will deepen our understanding of aging. Elucidating the mechanistic insights will facilitate the development of therapeutic agents that delay or attenuate age-related functional deterioration that occurs in multiple organs including the skin, heart, and brain, improving quality of life in the elderly and lessening the economic burden of age-related diseases.

Conclusions

Many molecular variants with age influence tissue-specific stem cell populations, residing in adult tissues such as the skin, liver, muscle and brain, in a way that leads to a progressive decline in regenerative capacity. Understanding the mechanisms underlying stem cell aging with the integrative approaches will enable us to make significant progress toward providing precision, preventive, and personalized medicine for aging.

Abbreviations

CR: Calorie restriction; Gln: Glutamine; iPSCs: Induced pluripotent stem cells; NSC: Neural stem cells; ROS: Reactive oxygen species; TCA: Tricarboxylic acid cycle; TOR: Target of rapamycin

Acknowledgements

We greatly appreciate the support received through the collaborative work undertaken between CHA University and McLean Hospital.

Funding

This work was supported by the National Research Foundation of Korea (NRF-2016R1A2B4007640) and (NRF-2017M3A9B4025699 and NRF-2017M3A9B4025709).

Availability of data and materials

Not applicable.

Authors' contributions

SHB and CHK designed the study and wrote the manuscript. PL revised the article. JM and KSK reviewed the study and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 15 February 2017 Accepted: 20 September 2017
Published online: 03 November 2017

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