BBA - Molecular Basis of Disease 1865 (2019) 1715–1717

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Preface

Genetics and Epigenetics in Aging and Longevity: Myths and Truths☆

Aging is an irreversible complex biological process, characterized by progressive decline in organismal function and increased vulnerability to chronic diseases including cardiovascular diseases, dementia, cancers, and metabolic diseases. With the increase in human lifespan, we are facing a rapidly growing aging population in our society and associated high health care burden [1]. To this end, how to best promote the healthy aging (healthspan) and longevity (lifespan) becomes an intimate issue for health care professionals. The search and identification of aging/longevity-associated genes and signal pathways such as Sirtuins have greatly assist us to unveil the molecular mechanisms underneath aging and healthspan [2,3]. Despite of the recent advancement in medicine and evidence-based therapies, unfavorable structural and functional changes develop in organs with time, culminating in the increased prevalence of diseases such as cardiovascular and chronic diseases (e.g., cancer and metabolic anomalies) in the elderly [1,4]. For example, ventricular dilatation, deterioration of cardiac function and reserve, endothelial dysfunction and hypertension develop with age to impose a high cardiovascular morbidity and mortality [2,3]. Up-to-date, several theories were postulated for biology of aging including the 'free radical theory of aging', the 'glycation theory of aging', the "evolutionary theory of aging", the 'replication theory of aging' and the 'telomerase length theory of aging' [4], to trigger adaptive and maladaptive organismal changes under the interactions of genes and environments. A better and thorough understanding of the complex genetic and epigenetic regulation of aging process and longevity should help to better develop new strategies to confront challenge brought forward by this irreversible biology process. Here we are presenting this special issue of "BBA Mol Basis Disease" on "Genetic and epigenetic regulation of aging and longevity". Our enthusiasm for this topic rooted from the profound prevalence of genetic and epigenetic cues for lifespan extension and health aging. Disruption of these genetic and epigenetic processes often leads to changes in the course of lifespan, with various pathological sequelae. To optimize the health care management in the elderly, it is imperative to improve our knowledge for genetic and epigenetic regulation of aging process and longevity. For example, chromatin connectivity is likely compromised with age, resulting in the displacement of constitutive heterochromatin by the senescence-associated heterochromatin, a process essential for aging [5]. This special series has gathered 20 clinical and experimental contributions from experts around the world discussing the current understanding of the mechanisms in the genetic and epigenetic regulation of aging and longevity, and the potential for targeting novel pathways to combat aging complications.

In the first article of this series, Morris, Willcox and Donlon summarized the latest data on genetic and epigenetic cues to human aging and longevity. While environmental and lifestyle factors play a pivotal role at younger ages, genetics seems to carry a more important weight in extreme old ages. These authors discussed ~57 lifespan genetic loci from genome-wide studies and highlighted the contribution of defective transcriptional and chromatin networks in cellular function, stress resistance and aging [5]. In the second article, Khan and colleagues revisited a number of model organisms including yeast, ciliate, nematode, arthropod, fish, rodent, primate and human to dissect the genetic cues of longevity in these species. They also compared the genetic contributions of longevity mechanisms including adrenergic system, insulin/IGF-1, and mTOR in these species [6]. In the third article of this series, Oien and Moskovitz discussed the genetic regulation of the methionine sulfoxide reductase system in relevance to longevity and age-related diseases [7]. Methionine oxidation of proteins and insufficient methionine sulfoxide reductase are commonly associated with aging-related diseases such as neurodegenerative disease and cancer [7]. In the fourth article, Jin and associates reviewed the contribution of long noncoding RNAs in aging and aging complications, and discussed the potentials of using long noncoding RNAs as biomarkers and potential therapeutic targets for aging-associated diseases [8]. Long noncoding RNAs belongs to a class of regulatory ncRNAs with transcript length > 200 nucleotides. These highly specific and low conservative regulators are believed to govern certain aging phenotypes and ultimately lifespan. In the next article by Yang and colleagues reported that miR-216a regulated telomerase activity and macrophage polarization during atherosclerosis progression. Their data revealed that miR-216a promoted telomerase activation in macrophages through the Smad3/NF-κB pathway [9]. In the sixth article of this section, Zhu and colleagues examined the influence of mitochondrial aldehyde dehydrogenase (ALDH2) deficiency on high-cholesterol diet-induced atherosclerotic plaque progression and vulnerability in ApoE$^{-/-}$ mice. Their results showed that plaque area was decreased while plaque instability was aggravated by ALDH2 deficiency. Further scrutiny revealed that ALDH2 deficiency acted through accelerating ROS-mediated VSMC senescence [10]. A unique cardioprotective role has been suggested for ALDH2 in cardiovascular homeostasis [11]. In this work, ALDH2 inhibited oxLDL-induced mitochondrial ROS production and activation of downstream p53/p21/p16 signaling cascades [10]. The seventh article by Ji's group revealed that oxLDL induced S-nitrosylation of eNOS, which promoted interaction between eNOS and β-catenin, transcriptional capacity of β-catenin, cell migration and adhesion in endothelial cells [12]. In the eighth article of this series, Sowers and colleagues reviewed a number of signaling pathways associated with

---

☆ This article is part of a Special Issue entitled: Genetic and epigenetic regulation of aging and longevity edited by Jun Ren & Megan Yingmei Zhang.

https://doi.org/10.1016/j.bbadis.2019.02.005

pathophysiological changes in endothelium including Sirtuin 1, Klotho, fibroblast growth factor 21 (FGF21), and renin angiotensin-aldosterone system. Their review has offered a contemporary viewpoint on the molecular mechanisms and pathophysiological changes in endothelial senescence and aging-associated cardiovascular disease [13]. In the next article, Chi and coworkers reported the current understanding on senescence of VSMCs and related aging disorders. The importance of VSMC senescence has been increasingly recognized in vascular aging [14]. In the 10th article of this series, Ma and colleagues discussed the benefits of the longevity gene sirtuins in regulating atherosclerotic cellular senescence, and the potentials of targeting sirtuins in therapeutics against atherosclerosis [15]. In the 11th article by Blice-Baum and colleagues, cardiovascular aging was recapitulated in Drosophila. Given the multi-faced cardiac functional deterioration with aging and the limitation of examining cardiac aging using human subjects or mammalians, *Drosophila melanogaster* mat serve as a powerful model to examine the molecular and genetic aspects of cardiac senescence in a short timeframe [16]. Likewise, Wang and coworkers discussed mitochondrial regulation of cardiac aging, molecular mechanisms behind anti-aging treatment, and the potential interventions that alleviate cardiac aging through regulation of mitochondria [17]. In the 13th article of this series, Wang and associates examined the impact of ablation of Akt2 (cardiac isoform of Akt) and AMPKα2 on the development of cardiac aging. Their results revealed that increased age (12 months) did not exhibit notable changes in cardiac geometry, contractile function, morphology, ultrastructure, and mitophagy, although Akt2-AMPK ablation predisposed age-induced unfavorable changes in geometry, TEM ultrastructure, and function. These data suggested that Akt2-AMPK double knockout predisposes cardiac aging related to compromised mitophagy [18]. In the next article by Linsey and colleagues, molecular and cellular indicators were tested to correlate with the extent of dilation of left ventricle following myocardial infarction in an effort to improve diagnostic and prognostic capabilities. Using the mHART 1.0 database, these authors concluded that insufficient macrophage-mediated inflammation is indicative for accentuated left ventricular dilation. Their study revealed a composite panel including plasma MIP-1γ, lymphotactin, and GCP-2, and left ventricular infarct Ccr8 and macrophage numbers to reflect left ventricular LV dilation [19]. Population-based and experimental data have suggested a close tie between age-related diseases (e.g., cardiac aging) and obesity. In the fifteenth article by Sun and coworkers, the authors discussed the contribution of autophagy failure in obesity-related cardiac aging, and how obesity may predispose the pre-matured cardiovascular aging [20]. Along the same line, increased prevalence of type 2 diabetes mellitus is commonly associated with aging, with diabetic microvascular complications (such as retinopathy and nephropathy] displaying some poor efficacy using classical glucose lowering drugs. Gut microbiota becomes a potential resource for therapeutics to modulate host immunity and metabolism. In the sixteenth article, Fernandes and colleagues provided an in-depth view on the crosstalk between gut microbiota and host immunity/metabolism, and how it characterizes human gut microbiota signatures of elderly and diabetic patients [21]. In the seventeen articles, Sun's research group demonstrated that systemic deletion of Mst1 gene rescues against diabetic cardiomyopathy through Parkin-mediated mitophagy. Mst1 disruption restores mitochondrial autophagy in diabetic heart [22]. In the next article, Zhai and coworkers detected that higher intracellular cholesterol levels due to loss of ATP-binding cassette A1 (ABCA1) stimulated the epithelial sodium channel (ENaC) in aging mice. This study implies that reduced ABCA1 level may mediate aging-associated hypertension by way of ENaC through elevation of intracellular cholesterol [23]. Given that elderly populations often suffer from inadequate intake of vitamins, folate and iron [24], Zhang and colleagues provided an overview of iron metabolism in the nineteenth article of the series. These authors discussed how iron disorders (both deficiency and overload) may promote heart failure and provide the clinical perspective on the treatment options for iron metabolism disorders [25]. In the last article of the series, Lee and colleagues discussed how EWSR1 (Ewing Sarcoma breakpoint region 1/EWS RNA binding protein 1) regulates organismal function and aging through genetic and epigenetic pathways [26]. Recent evidence revealed a role for EWSR1 mutation in central nervous disorders including amyotrophic lateral sclerosis and frontotemporal dementia [27]. Therefore, a better description of the bona fide role of EWSR1 should help to better manage aging and its association with brain disorders.

Although this special issue should help to improve our knowledge in the race to identify genetic and epigenetic cues for aging and longevity, the topics described here may have raised more questions than answers. For example, while it is somewhat practical to monitor organ and cellular function, whether these genetic and epigenetic regulations also affect lifespan remain a mystery in higher species. Next, animal or cell models for human aging suffer from limitations to recapitulate the pathological changes under authentic clinical settings. In particular, some closely related species may display drastic difference in lifespan. A typical rat survives for 5 years while the naked-mole rat can live to 30 years. Even within the same species, drastic variation can be seen for the rate of aging and lifespan (such as the queen and worker honey bees) [4]. Therefore, it is rather difficult to pinpoint which particular genetic or epigenetic alteration will be superior in dictating aging and longevity. We hope that this special series will help us to accelerate the race for ultimate identification of the genetic and epigenetic control of aging and longevity.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgement

The authors received support in part from Natural Science Foundation of China No. 81522004 and No. NSFC 91749128.

References

[1] B.N. Ames, Prolonging healthy aging: longevity vitamins and proteins, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) 10836–10844.

[2] J. Ren, J.R. Sowers, Y. Zhang, Metabolic stress, autophagy, and cardiovascular aging: from pathophysiology to therapeutics, Trends Endocrinol. Metab. 29 (2018) 699–711.

[3] J. Ren, Y. Zhang, Targeting autophagy in aging and aging-related cardiovascular diseases, Trends Pharmacol. Sci. 39 (2018) 1064–1076.

[4] K. Zainabadi, A brief history of modern aging research, Exp. Gerontol. 104 (2018) 35–42.

[5] B.J. Morris, B.J. Willcox, T.A. Donlon, Genetic and epigenetic regulation of human aging and longevity, Biochim. Biophys. Acta Mol basis Dis. (2019).

[6] A.H. Khan, Z. Zou, Y. Xiang, S. Chen, X.-L. Tian, Conserved signaling pathways genetically associated with longevity across the species, Biochim. Biophys. Acta (2019).

[7] D.B. Oien, J. Moskovitz, Genetic regulation of longevity and age-associated diseases through the methionine sulfoxide reductase system, Biochim. Biophys. Acta (2019).

[8] L. Jin, Q. Song, W. Zhang, B. Geng, J. Cai, Roles of long noncoding RNAs in aging and aging complications, Biochim. Biophys. Acta (2019).

[9] S. Yang, J. Li, Y. Chen, S. Zhang, C. Feng, Z. Hou, J. Cai, Y. Wang, R. Hui, B. Lv, W. Zhang, MicroRNA-216a promotes M1 macrophages polarization and atherosclerosis progression by activating telomerase via the Smad3/NF-kappaB pathway, Biochim. Biophys. Acta Mol. basis Dis. (2018).

[10] H. Zhu, Z. Wang, Z. Dong, C. Wang, Q. Cao, F. Fan, J. Zhao, X. Liu, M. Yuan, X. Sun, X. Peng, Y. Zou, J. Zhou, J. Ge, X. Zhou, Y. Zhang, Aldehyde dehydrogenase 2 deficiency promotes atherosclerotic plaque instability through accelerating mitochondrial ROS-mediated vascular smooth muscle cell senescence, Biochim. Biophys. Acta Mol. basis Dis. (2018).

[11] Y. Zhang, J. Ren, ALDH2 in alcoholic heart diseases: molecular mechanism and clinical implications, Pharmacol. Ther. 132 (2011) 86–95.

[12] W. Wang, D. Wang, C. Kong, S. Li, L. Xie, Z. Lin, Y. Zheng, J. Zhou, Y. Han, Y. Ji, eNOS S-nitrosylation mediated OxLDL-induced endothelial dysfunction via increasing the interaction of eNOS with betacatenin, Biochim. Biophys. Acta Mol. basis Dis. (2018).

[13] J. G, A.R. Aroor, C. Jia, J.R. Sowers, Endothelial cell senescence in aging-related vascular dysfunction, Biochim Biophys Acta (2019).

[14] C. Chi, D.-J. Li, Y.-J. Jiang, J. Tong, H. Fu, Y.-H. Wu, F.-M. Shen, Vascular smooth muscle cell senescence and age-related diseases: state of the art, Biochim. Biophys. Acta (2019).

[15] S. Ma, L. Fan, F. Cao, Combating cellular senescence by sirtuins: implications for atherosclerosis, Biochim. Biophys. Acta Mol. basis Dis. (2018).

[16] A.C. Blice-Baum, M.C. Guida, P.S. Hartley, P. Adams, R. Bodmer, A. Cammarato, As time flies by: investigating cardiac aging in the short-lived Drosophila model, Biochim Biophys Acta Mol Basis Dis (2019).

[17] Y. Wang, Y. Li, C. He, B. Gou, M. Song, Mitochondrial regulation of cardiac aging, Biochim. Biophys. Acta (2019).

[18] S. Wang, M.R. Kandadi, J. Ren, Double knockout of Akt2 and AMPK predisposes cardiac aging without affecting lifespan: role of autophagy and mitophagy, Biochimica et Biophysica Acta (2019) (xx-yy).

[19] M.L. Lindsey, Y. Ma, E.R. Flynn, M.D. Winniford, M.E. Hall, K.Y. DeLeon-Pennell, Identifying the molecular and cellular signature of cardiac dilation following myocardial infarction, Biochim. Biophys. Acta (2019).

[20] M. Sun, Y. Tan, M. Rexiati, M. Dong, W. Guo, Obesity is a common soil for premature cardiac aging and heart diseases — role of autophagy, Biochim. Biophys. Acta (2019).

[21] R. Fernandes, S.D. Viana, S. Nunes, F. Reis, Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy, Biochim. Biophys. Acta Mol. basis Dis. (2018).

[22] S. Wang, Z. Zhao, Y. Fan, M. Zhang, X. Feng, J. Lin, J. Hu, Z. Cheng, C. Sun, T. Liu, Z. Xiong, Z. Yang, H. Wang, D. Sun, Mst1 inhibits Sirt3 expression and contributes to diabetic cardiomyopathy through inhibiting Parkin-dependent mitophagy, Biochim. Biophys. Acta Mol. basis Dis. (2018).

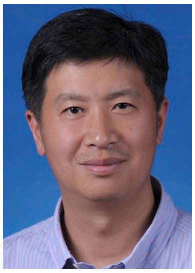
[23] Y.-J. Zhai, M.-M. Wu, V.A. Linck, L. Zou, Q. Yue, S.-P. Wei, C. Song, S. Zhang, C.R. Williams, B.-L. Song, Z.-R. Zhang, H.-P. Ma, Intracellular cholesterol stimulates ENaC by interacting with phosphatidylinositol-4,5-bisphosphate and mediates cyclosporine A-induced hypertension, Biochim Biophys Acta (2019).

[24] J. Watson, M. Lee, M.N. Garcia-Casal, Consequences of inadequate intakes of vitamin a, vitamin B12, vitamin D, calcium, Iron, and folate in older persons, Curr Geriatr Rep 7 (2018) 103–113.

[25] H. Zhang, P. Zhabyeyev, S. Wang, G.Y. Oudit, Role of iron metabolism in heart failure: from iron deficiency to iron overload, Biochim. Biophys. Acta (2019).

[26] J. Lee, P.T. Nguyen, H.-S. Shim, S.J. Hyeon, H. Im, M.-H. Choi, S. Chung, N. Kowall, S.B. Lee, H. Ryu, EWSR1, a multifunctional protein, regulates cellular function and aging via genetic and epigenetic pathways, Biochim. Biophys. Acta (2019).

[27] D. Orozco, D. Edbauer, FUS-mediated alternative splicing in the nervous system: consequences for ALS and FTLD, J Mol Med (Berl) 91 (2013) 1343–1354.



Jun Ren, MD, PhD, FAHA, is a Professor of Pharmacology at the University of Wyoming College of Health Sciences (Laramie, USA) and also as Professor in the Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China. He earned his Ph.D. in 1994 from the University of Alberta, Canada, in the area of cellular physiology, following his medical training in China (Beijing University and Peking Union Medical College). In 1994, he became a post-doctoral fellow in theWayne State University School of Medicine (Internal Medicine), where he served for two years. He remained at Wayne State University until 1998, working as a research instructor of physiology. He was an Assistant Professor of Physiology at the University of North Dakota School of Medicine and Health Sciences from 1998 to 2002 and then an Associate Professor of University of Wyoming from 2002 to 2005. He was promoted to full professor in 2005 and served as Associate Dean for Research in the College of Health Sciences at the University of Wyoming in 2008–2016. His major area of research is related to cardiac pathophysiology in alcoholism, diabetes, obesity and aging. His research was funded by the American Heart Association, American Diabetes Association, NIH and Natural Science Foundation of China. He has been an editor or on editorial board for a number of journals including Diabetes, Hypertension, BBA Molecular Basis of Disease, Journal of Molecular and Cellular Cardiology, American Journal of Physiology, Cardiovascular Toxicology and Clinical and Experimental Pharmacology and Physiology.

Yingmei Zhang, M.D., Ph.D. FACC, is a Professor of Cardiology and Attending Cardiologist in the Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China. She also serves as an adjunct Assistant Professor in the College of Health Science at the University of Wyoming. She is a Yangtze River scholar Professor (Youth Scholar Program) and a winner of National Science Fund for Excellent Young Scholars. Prof. Zhang is also a member of Basic Research Group in the Chinese medical association cardiovascular branch. She received her Master's and doctoral degrees from the Fourth Military Medical University and completed post-doctoral training at the University of Wyoming. She has over 80 publications in the area of pathogenesis and therapeutics of myocardial dysfunction focusing on the regulation of mitochondrial function and autophagy. Her research has been supported by the Natural Science Foundation of China, and National Institute of Health (NIH). She serves as an editor or on editorial board for several scientific journals including BBA Molecular Basis of Disease. Her scientific contributions encompass (1) revealing mechanism(s) of myocardial mitochondrial injury; (2) depicting the beneficial role for endogenous myocardial proteins including mitochondrial aldehyde dehydrogenase (ALDH2); in metabolic diseases.

Jun Ren, Yingmei Zhang*
Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, 210032, PR China
Center for Cardiovascular Research and Alternative Medicine, University of Wyoming, Laramie, WY 82071, USA
E-mail addresses: jren@uwyo.edu (J. Ren), zhangym197951@126.com (Y. Zhang).

---

* Corresponding author at: Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai 210032, PR China.