

Contents lists available at [ScienceDirect](http://ScienceDirect.com)

Biochimica et Biophysica Acta

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

Preface

Emerging potential of therapeutic targeting of autophagy and protein quality control in the management of cardiometabolic diseases[☆]



We are delighted and thrilled to serve as editors for this special issue of “*BBA Mol Basis Disease*” on “Autophagy and protein quality control in cardiometabolic disease”. Our enthusiasm for this special topic rooted from the profound protein damage in individuals with cardiovascular diseases in particular ischemic/reperfusion injury, diabetes mellitus, insulin resistance, obesity and hypertension [1–4]. Although recent advances in medical technology and health care have drastically improved the success of early diagnosis and management for cardiovascular diseases, the ever-rising prevalence for metabolic issues including obesity, diabetes mellitus, insulin resistance, hypertension and dyslipidemia, collectively known as cardiometabolic diseases, continues to serve as main contributing risk factors for cardiovascular morbidity and mortality in our modern society [1,5]. Despite numerous available studies and clinical trials in the field of cardiometabolic diseases, the underlying pathological mechanisms remain essentially elusive for these comorbidities, which hinder the appropriate management of cardiovascular events [6–8]. Up-to-date, a number of theories have been put forward for the pathogenesis of cardiometabolic disease including insulin resistance, abnormal glucose and lipid metabolism, oxidative and nitrosative/nitrative stress, endoplasmic reticulum (ER) stress, apoptosis, mitochondrial damage, low-grade inflammation, and the satiety lifestyle [1,5,9,10]. More recent evidence suggests an essential role for proteotoxicity, which refers to the detrimental effects of damaged proteins for cells and organisms, in cardiovascular in particular cardiometabolic diseases [11]. Protein quality control is governed mainly by the ubiquitin–proteasome system (UPS) and autophagy–lysosomal pathways, representing two major although distinct cellular machineries for the degradation and removal of most proteins [3,11]. UPS degrades the majority of proteins, whereas autophagy is a highly conserved process by which intracellular components, including soluble macromolecules (e.g. nucleic acids, proteins, carbohydrates, lipids) and defective organelles (e.g. mitochondria, ribosomes, peroxisomes, and ER) are degraded by the lysosome. Disruption of these processes triggers pathological sequelae, leading to proteotoxic alterations in cardiovascular diseases such as idiopathic, hypertrophic, ischemic, and pressure-overloaded cardiomyopathies [2,11]. To optimize effective therapeutic regimes, it is imperative to better our understanding for the precise role for protein quality control in the onset and pathogenesis of cardiometabolic syndrome. This special issue of “*BBA Molecular Basis Disease*” tackles some of the burning issues on protein quality control through

machineries of autophagy and UPS in the pathogenesis and therapeutics of cardiometabolic disease.

In the first article of this series, Wang and Wang reviewed the current understanding for the role of UPS and autophagy in the regulation of cardiac proteotoxicity, and then addressed crosstalk mechanism between these two pathways. Although UPS and autophagy are distinct protein degradation pathways (e.g., small versus large molecules), crosstalk exists between these two degradation machineries. Proteasomal inhibition activates autophagy. However, autophagy inhibition elicits somewhat complex effect on proteasome peptidase activities depending on the duration of suppressed autophagy [2]. In the second article, Hua and Nair discussed the promises of targeting major proteases including matrix metalloproteinase (MMP), cathepsins, calpains and caspases in the therapeutics of cardiometabolic diseases. Elevated levels and/or activities of proteases have been documented in atherosclerosis, coronary heart disease, obesity and insulin resistance, concurrent with the application of proteases as key biomarkers for cardiometabolic diseases. Hua and Nair further discussed the salutary effects and potential mechanisms behind protease inhibitors in cardiometabolic diseases [12]. In the third article, Yang and her colleagues tackled the interplay between ER stress and protein quality control in diabetic cardiomyopathy. ER stress, an early event found in diabetic cardiomyopathy, may be triggered by hyperglycemia, free fatty acids (FFAs) and inflammation. These authors discussed how ER stress in response to these triggers may interfere with ER integrity, autophagy, and ultimately development of diabetic cardiomyopathy [13]. The fourth article by Sowers and coworkers thoroughly discussed potential contribution of dysregulated autophagy in the development of cardiorenal metabolic syndrome, including insulin resistance, obesity, hypertension, maladaptive immunity. The authors dissected how cellular protein quality control by way of the disposal and recycling of cellular components might participate in the pathogenesis of cardiorenal metabolic syndrome [14]. The fifth article by Xu and colleagues discussed how autophagy is involved in the regulation of cardiac function in cardiometabolic syndrome. They discussed the therapeutic potential of targeting autophagy in the management of cardiac complications under metabolic anomalies such as diet-induced obesity [15]. In the next article, Varga and colleagues provided insights into the complex interplay of oxidative/nitrosative stress *en route* to pro-inflammatory and pro-apoptotic outcomes in the pathogenesis of diabetic cardiomyopathy. They went on to discuss how superoxide produced by mitochondria, NADPH oxidases and xanthine oxidoreductase may interact with nitric oxide (NO) to form the potent toxin peroxynitrite, to turn on stress kinases, ER stress, mitochondrial and

[☆] Preface for the BBA Mol Basis Disease Special Issue – “Autophagy and protein quality control in cardiometabolic diseases”.

poly(ADP-ribose) polymerase 1-dependent cell death. As a result, the autophagy/mitophagy homeostasis is interrupted, leading to impaired protein control for myocardial Ca^{2+} handling, contractility, antioxidant defense, MMP and pro-inflammatory transcription factors, which all contribute to the development of diabetic cardiomyopathy [16]. In the seventh article, Mei and colleagues further elucidated the delicate interplay between oxidative stress and autophagy. They emphasized the dual regulatory (double-edged sword) role for autophagy in the cardiovascular homeostasis. Full appreciation of autophagy as either adaptive or maladaptive response provides potential new strategies for the prevention and management of cardiovascular diseases [17]. In the eighth article, Kobayashi and Liang discussed the unique role of mitophagy, or elimination of damaged mitochondria through autophagy, in myocardial mitochondrial injury in diabetes. They dissected the disparate roles for autophagy in particular mitophagy in type 1 and type 2 diabetes, suggesting an adaptive role for the diminished autophagy in cardiac injury associated with type 1 diabetes [18]. In the ninth article, Xu and colleagues examined the role of mitochondrial c-Jun N-terminal kinase (JNK) in ischemic heart injury. These investigators reported that activation of mitochondrial JNK, rather than localization of JNK on mitochondria, may induce autophagy and apoptosis to aggravate ischemia/reperfusion injury [19]. In the next article of this series, Ma and colleagues succinctly dissected the compelling dual roles for autophagy in ischemia-reperfusion injury. These authors elaborated the cellular mechanisms underneath beneficial and detrimental effects of autophagy in the pathology of cardiac ischemia reperfusion injury [20].

In the second half of this special series, the impact of a number of enzymes or proteins on homeostasis of autophagy, protein quality control, structure and function was addressed. In the first article, Bouhidel and colleagues reported cardioprotection offered by a novel protein netrin-1 in ischemia-reperfusion injury. Their finding revealed that the netrin-1-offered beneficial effect is mediated through the receptor from the deleted in colorectal cancer (DCC) and NO-dependent preservation of mitochondria while attenuating autophagy, suggesting the therapeutic potential of netrin-1 for myocardial infarction (MI) and post-MI remodeling [21]. In the second article, Roe and colleagues generated a cardiomyocyte-specific knockout of phosphatase and tensin homologue deleted from chromosome 10 (PTEN). Their work suggested a role for the loss of Pink1-AMPK signaling, interrupted autophagy and autophagic flux in the development of cardiac hypertrophy and contractile defect [22]. In the third article, Kandadi and coworkers examined another protein phosphatase namely protein tyrosine phosphatase-1B (PTP1B), a negative regulator of insulin signaling, in high fat diet-induced obesity. These authors reported that high fat diet compromised cardiac function, promoted cardiac remodeling and lipid accumulation, which were attenuated by PTP1B knockout. PTP1B knockout reversed high fat diet-induced loss of autophagy likely via an AMPK-dependent mechanism [23]. In the fourth article, Shen and colleagues reported that deficiency in mitochondrial aldehyde dehydrogenase (ALDH2), which is common in subsets of human population, exacerbated aortic constriction-induced cardiac defect and loss of autophagy. These data indicate that ALDH2 enzymatic deficiency may worsen pressure overload-induced cardiac dysfunction partly by inhibition of Beclin-1-dependent autophagy [24], which presents unique clinical relevance. The fifth article of this series also addressed the autophagy regulatory role of ALDH2 in diabetes where ALDH2 transgene rescued the heart against diabetic cardiomyopathy (compromised function and cardiac hypertrophy) along with facilitated autophagy. Inhibition of autophagy and AMPK mitigated ALDH2-offered beneficial effect, suggesting a possible role of autophagy in ALDH2-offered protection against diabetes [25]. These work using experimental pressure overload and diabetic models favor a unique cardioprotective role for the mitochondrial chaperon ALDH2 through facilitated cardiac autophagy. In the sixth article of this series, Zheng and colleagues examined the role of the essential energy fuel signal AMPK in prolonged caloric restriction-induced change in the maintenance of cardiac homeostasis.

Caloric restriction may compromise echocardiographic function, cardiomyocyte contractile and intracellular Ca^{2+} properties in association with upregulated autophagy. Interestingly, AMPK inhibition reversed caloric restriction-induced changes in autophagy and autophagy signaling. AMPK inhibition led to dampened autophagy, suggesting an indispensable role for AMPK in the maintenance of cardiac homeostasis under caloric restriction [26]. Given that the master energy fuel regulator AMPK helps to promote energy supply and cut down anabolism, it is reasonable to speculate the indispensable role for AMPK in the maintenance of cardiac homeostasis under starvation. In the seventh article of this series, Liang and colleagues examined the role of the antioxidant catalase in fat diet-induced changes in cardiac autophagy, geometry and function. Myocardial geometry and function were compromised with fat diet intake, the effects of which were ameliorated by catalase. High fat diet intake promoted reactive oxygen species (ROS) generation and suppressed autophagy in the heart, the effects of which were attenuated by catalase, possibly via an IKK β -AMPK-dependent restoration of myocardial autophagy [27]. In the eighth article of this section, Yan and colleagues examined the role of a novel cellular repressor of E1A gene (Creg1), an evolutionarily conserved lysosomal protein, in myocardial fibrosis in the face of aging or angiotensin II (Ang II) exposure. These authors observed accumulation of autophagosomes and interruption of autophagic flux under Creg1 deficiency, depicting a unique role for Creg1 as a viable therapeutic target for pathological cardiac conditions [28]. In the last article of this series, Zhao and Li reviewed the role of the interferon-regulatory factor (IRF) transcriptional factor family in the regulation of cell survival processes such as metabolism. These authors discussed the novel stress-responsive regulatory role for IRFs [29].

Although the collections in this special issue have shed some insights toward the better understanding of autophagy and protein quality control in the regulation of cardiac homeostasis in cardiometabolic diseases, it is noteworthy that the topics described here probably raise more questions than answers. First, given the availability of genetically engineered murine models of autophagy, it is desirable to conduct a "proof of concept" type of research in cardiometabolic diseases. Second, like all animal models, animal or cell models for human cardiometabolic disease suffer from limitation to mimic the scope of pathological changes under the clinical cardiometabolic syndrome setting. Special caution needs to be taken to employ the bench-side concept to the bed-side practice. Third, given the complexity in the etiology of cardiometabolic diseases, it remains challenging to pinpoint which intervention targeting autophagy may be more superior. We hope that this special series will help identify novel therapeutic targets to launch better intervention regimens for the management of cardiometabolic diseases.

References

1. Onat, Metabolic syndrome: nature, therapeutic solutions and options, *Expert Opin. Pharmacother.* 12 (2011) 1887–1900.
2. C. Wang, X. Wang, The interplay between autophagy and the ubiquitin-proteasome system in cardiac proteotoxicity, *Biochim. Biophys. Acta* 1852 (2015) 188–194 [in this issue].
3. B.C. Hammerling, A.B. Gustafsson, Mitochondrial quality control in the myocardium: cooperation between protein degradation and mitophagy, *J. Mol. Cell. Cardiol.* 75C (2014) 122–130.
4. A. Pawlak, J. Bil, R.J. Gil, The regulatory mechanisms of protein expression in heart failure patients' cardiomyocytes. The ubiquitin-proteasome system. *Autophagy, Kardiol. Pol.* 70 (2012) 1170–1176.
5. J. Kaur, A comprehensive review on metabolic syndrome, *Cardiol. Res. Pract.* 2014 (2014) 943162.
6. C.P. Cannon, A. Kumar, Treatment of overweight and obesity: lifestyle, pharmacologic, and surgical options, *Clin Cornerstone* 9 (2009) 55–68 (discussion 9–71).
7. K.G. Alberti, R.H. Eckel, S.M. Grundy, P.Z. Zimmet, J.I. Cleeman, K.A. Donato, et al., Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity, *Circulation* 120 (2009) 1640–1645.
8. M.A. Cornier, D. Dabelea, T.L. Hernandez, R.C. Lindstrom, A.J. Steig, N.R. Stob, et al., The metabolic syndrome, *Endocr. Rev.* 29 (2008) 777–822.
9. J. Ren, R.O. Kelley, Cardiac health in women with metabolic syndrome: clinical aspects and pathophysiology, *Obesity (Silver Spring)* 17 (2009) 1114–1123.

- [10] J. Ren, L. Pulakat, A. Whaley-Connell, J.R. Sowers, Mitochondrial biogenesis in the metabolic syndrome and cardiovascular disease, *J. Mol. Med.* 88 (2010) 993–1001.
- [11] M. Sandri, J. Robbins, Proteotoxicity: an underappreciated pathology in cardiac disease, *J. Mol. Cell. Cardiol.* 71 (2014) 3–10.
- [12] Y. Hua, S. Nair, Proteases in cardiometabolic diseases: pathophysiology, molecular mechanisms and clinical applications, *Biochim. Biophys. Acta* 1852 (2015) 195–208 [in this issue].
- [13] L. Yang, D. Zhao, J. Ren, J. Yang, Endoplasmic reticulum stress and protein quality control in diabetic cardiomyopathy, *Biochim. Biophys. Acta* 1852 (2014) 209–218 [in this issue].
- [14] G. Jia, J.R. Sowers, Autophagy: a housekeeper in cardiorenal metabolic health and disease, *Biochim. Biophys. Acta* 1852 (2015) 219–224 [in this issue].
- [15] S.Y. Ren, X. Xu, Role of autophagy in metabolic syndrome-associated heart disease, *Biochim. Biophys. Acta* 1852 (2015) 225–231 [in this issue].
- [16] Z.V. Varga, Z. Giricz, L. Liaudet, G. Hasko, P. Ferdinandy, P. Pachter, Interplay of oxidative, nitrosative/nitrative stress, inflammation, cell death and autophagy in diabetic cardiomyopathy, *Biochim. Biophys. Acta* 1852 (2015) 232–242 [in this issue].
- [17] Y. Mei, M.D. Thompson, R.A. Cohen, X. Tong, Autophagy and oxidative stress in cardiovascular diseases, *Biochim. Biophys. Acta* 1852 (2015) 243–251 [in this issue].
- [18] S. Kobayashi, Q. Liang, Autophagy and mitophagy in diabetic cardiomyopathy, *Biochim. Biophys. Acta* 1852 (2015) 252–261 [in this issue].
- [19] J. Xu, X. Qin, X. Cai, L. Yang, Y. Xing, J. Li, et al., Mitochondrial JNK activation triggers autophagy and apoptosis and aggravates myocardial injury following ischemia/reperfusion, *Biochim. Biophys. Acta* 1852 (2015) 262–270 [in this issue].
- [20] S. Ma, Y. Wang, Y. Chen, F. Cao, The role of the autophagy in myocardial ischemia/reperfusion injury, *Biochim. Biophys. Acta* 1852 (2015) 271–276 [in this issue].
- [21] J.O. Bouhidel, P. Wang, K.L. Siu, H. Li, J.Y. Youn, H. Cai, Netrin-1 improves post-injury cardiac function *in vivo* via DCC/NO-dependent preservation of mitochondrial integrity, while attenuating autophagy, *Biochim. Biophys. Acta* 1852 (2015) 277–289 [in this issue].
- [22] N.D. Roe, X. Xu, M.R. Kandadi, N. Hu, J. Pang, M.C.M. Weiser-Evans, et al., Targeted deletion of PTEN in cardiomyocytes renders cardiac contractile dysfunction through interruption of Pink1–AMPK signaling and autophagy, *Biochim. Biophys. Acta* 1852 (2015) 290–298 [in this issue].
- [23] M.R. Kandadi, E. Panzhinskiy, N.D. Roe, S. Nair, D. Hu, A. Sun, Deletion of protein tyrosine phosphatase 1B rescues against myocardial anomalies in high fat diet-induced obesity: role of AMPK-dependent autophagy, *Biochim. Biophys. Acta* 1852 (2015) 299–309 [in this issue].
- [24] C. Shen, C. Wang, F. Fan, Z. Yang, Q. Cao, X. Liu, et al., Acetaldehyde dehydrogenase 2 (ALDH2) deficiency exacerbates pressure overload-induced cardiac dysfunction by inhibiting Beclin-1 dependent autophagy pathway, *Biochim. Biophys. Acta* 1852 (2015) 310–318 [in this issue].
- [25] Y. Guo, W. Yu, D. Sun, J. Wang, C. Li, R. Zhang, et al., A novel protective mechanism for mitochondrial aldehyde dehydrogenase (ALDH2) in type I diabetes-induced cardiac dysfunction: role of AMPK-regulated autophagy, *Biochim. Biophys. Acta* 1852 (2015) 319–331 [in this issue].
- [26] Q. Zheng, K. Zhao, X. Han, A.F. Huff, Q. Cui, S.A. Babcock, et al., Inhibition of AMPK accentuates prolonged caloric restriction-induced change in cardiac contractile function through disruption of compensatory autophagy, *Biochim. Biophys. Acta* 1852 (2015) 332–342 [in this issue].
- [27] L. Liang, X.L. Shou, H.K. Zhao, G.Q. Ren, J.B. Wang, X.H. Wang, et al., Antioxidant catalase rescues against high fat diet-induced cardiac dysfunction via an IKK β -AMPK-dependent regulation of autophagy, *Biochim. Biophys. Acta* 1852 (2015) 343–352 [in this issue].
- [28] C.H. Yan, Y. Li, X.X. Tian, N. Zhu, H.X. Song, J. Zhang, et al., PrcREG1 upregulates Rab7 expression to activate autophagy and ameliorate cardiac damage, *Biochim. Biophys. Acta* 1852 (2014) 353–364 [in this issue].
- [29] G.N. Zhao, D.S. Jiang, H. Li, Interferon regulatory factors: at the crossroads of immunity, metabolism, and disease, *Biochim. Biophys. Acta* 1852 (2015) 365–378 [in this issue].



Jun Ren is a Professor of Pharmacology at the University of Wyoming College of Health Sciences. 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 the Wayne 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 1998–2002 and then an Associate Professor of University of Wyoming from 2002–2005. He was promoted to full professor in 2005 and was appointed as Associate Dean for Research in the College of Health Sciences at the University of Wyoming in 2008. His major area of research is related to cardiac pathophysiology in alcoholism, diabetes, obesity and aging. His research has been funded by the American Heart Association, American Diabetes Association and NIH. He is editor or on editorial board for a number of journals including *Diabetes*, *Journal of Molecular and Cellular Cardiology*, *American Journal of Physiology*, *Cardiovascular Toxicology* and *Clinical and Experimental Pharmacology and Physiology*.



Yingmei Zhang, is an Associate Professor and Attending Cardiologist in the Department of Cardiology, Xijing Hospital, the Fourth Military Medical University. She also serves as an adjunct Assistant Professor in the College of Health Science at the University of Wyoming. She received her Master's and doctoral degrees from the Fourth Military Medical University and completed post-doctoral training at the University of Wyoming in 2012. She has over 40 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, National Institute of Health (NIH) and American Diabetes Association (ADA). She serves as an editor or on editorial

board for several scientific journals. Her scientific contributions encompass (1) revealing mechanism(s) behind myocardial mitochondrial injury under ER stress; (2) depicting the beneficial role for endogenous myocardial proteins including mitochondrial aldehyde dehydrogenase (ALDH2) and insulin-like growth factor I (IGF-1) under metabolic syndrome.

Jun Ren*

Yingmei Zhang*

Center for Cardiovascular Research and Alternative Medicine, University of Wyoming, Laramie, WY 82071, USA

*Corresponding authors at: University of Wyoming College of Health Sciences, Laramie, WY 82071, USA. Tel.: +1 307 766 6131; fax: +1 307 766 2953.

E-mail addresses: jren@uwyo.edu (J. Ren), yingmeimegzhang@gmail.com (Y. Zhang).