JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 4, NO. 2, 2019

EDITORIAL COMMENT

Nuclear Hmgb1

The Fix for the Failing Heart*

Angela Raucci, PhD,[a] Maurizio C. Capogrossi, MD[b,c]

Heart failure (HF) represents the final common pathway of different forms of heart disease, it affects patients across a broad age range, and its prevalence increases dramatically in the elderly population. Cardiomyocyte hypertrophy and cardiac fibrosis are hallmarks of HF (1). The mechanisms underlying the development and progression of different forms of HF remain an area of active investigation. The paper by Takahashi et al. (2) in this issue of *JACC: Basic to Translational Science* provides novel insights on the effect of high-mobility group box 1 protein (HMGB1) on deoxyribonucleic acid (DNA) damage response (DDR) in a mouse model of HF induced by chronic infusion of angiotensin II (Ang II).

SEE PAGE 234

DNA damage is induced by several insults, and DDR, which consists of a sophisticated network of signaling pathways involving cell cycle checkpoints, the DNA repair machinery, and transcriptional programs, is activated to restore the altered DNA and avoid genotoxic stress (3). The ataxia telangiectasia-mutated (ATM) kinase is 1 of the best-characterized DDR transducers, able to phosphorylate multiple DDR mediators, including the histone variant H2AX and the tumor suppressor p53, necessary to stop cell cycle and repair the DNA (4). If the repair fails, cells undergo apoptosis or cell cycle arrest and senescence (5).

DDR is observed also in post-mitotic cells such as cardiomyocytes, and its prolonged activation promotes apoptosis and detrimental cardiac remodeling after myocardial infarction (6,7). Persistent DDR plays a role in the pathogenesis of HF as well, and various types of damage, including oxidative DNA damage and DNA single- and double-strand breaks, have been found in cardiomyocytes of patients with end-stage HF and in the hearts of mice with cardiac hypertrophy induced by transverse aortic constriction or Ang II infusion (7–9). Genetic reduction of ATM attenuates left ventricular dysfunction and improves mortality in mice that underwent transverse aortic constriction by reducing nuclear factor-κB-mediated cardiac inflammation (8). Cardiomyocyte-specific genetic ablation or pharmacological inhibition of ATM reduces cardiac hypertrophy by preventing calcineurin expression and eukaryotic translation initiation factor 4E-binding protein 1 phosphorylation (9).

HMGB1 is a nonhistone chromatin protein involved in transcription regulation, DNA replication and repair, and nucleosome assembly (10–12). HMGB1 can be passively released by damaged cells or actively secreted by stressed immune cells and, once in the extracellular environment, it acts as an endogenous "alarmin" promoting inflammation or tissue repair and regeneration (13). Exogenous HMGB1 reduces cardiomyocyte contractility and induces hypertrophy and apoptosis, stimulates cardiac fibroblast activity, and cardiac stem cell proliferation and differentiation. Inhibitors of extracellular HMGB1 exert a protective function in experimental models of

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Unit of Experimental Cardio-Oncology and Cardiovascular Aging, Centro Cardiologico Monzino-IRCCS, Milan, Italy; [b]Division of Cardiology, Johns Hopkins Bayview Medical Center, Baltimore, Maryland; and the [c]Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, Baltimore, Maryland.
This work was supported by Fondazione Cariplo (Research on Ageing diseases-2015) and Centro Cardiologico Monzino-IRCCS (Ricerca Corrente 2019) to Dr. Raucci. Dr. Capogrossib has reported that he has no relationships relevant to the contents of this paper to disclose.
All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2019.03.008

myocardial ischemia/reperfusion and in cardiomyopathies induced by mechanical stress, diabetes, infection, or chemotherapeutic drugs, mainly by reducing inflammation. In contrast, administration of recombinant HMGB1 after myocardial infarction induced by permanent coronary artery ligation promotes cardiac regeneration and preserves left ventricular function (14,15). Notably, mice overexpressing HMGB1 in cardiomyocytes (HMGB1-Tg) are protected from cardiac damage induced by myocardial infarction, genotoxic drugs, and hypertrophic stimuli, and maintenance of high levels of nuclear HMGB1 inhibits cardiomyocyte apoptosis (16–18). Thus, HMGB1 may play both beneficial and detrimental functions after a cardiac injury depending on the specific experimental model and its subcellular localization.

In the paper by Takahashi et al. (2), the authors identify a previously unknown mechanism by which nuclear HMGB1 prevents pathologic cardiac hypertrophy. The study starts with the intriguing observation that nuclear HMGB1 decreases and phosphorylation of ATM (p-ATM) and γ-H2AX expression increase in failing human hearts. Furthermore, nuclear HMGB1 levels in cardiomyocytes inversely correlate with cell hypertrophy, cardiac fibrosis, and brain natriuretic peptide serum levels. Lower HMGB1 content favors HF progression because preservation of high levels of nuclear HMGB1 in cardiomyocytes protects against pathologic cardiac remodeling. Indeed, HMGB1-Tg mice exhibit an attenuation of Ang II–mediated hypertrophy and fibrosis along with a reduction of the Ang II–induced increase in interventricular septum diameter and posterior wall diameter, and decrease of early to atrial wave ratio. Interestingly, the authors show that HMGB1 prevents detrimental DDR activation *in vivo* because Ang II–treated hearts of HMGB1-Tg mice exhibit lower levels of p-ATM and γ-H2AX compared with wild-type mice. Consistently, Ang II reduces the expression of HMGB1 before inducing p-ATM and γ-H2AX activation in isolated neonatal rat cardiomyocytes (NRCMs). In these cells, HMGB1 overexpression attenuates Ang II–mediated hypertrophic growth; in contrast, HMGB1 silencing enhances p-ATM and γ-H2AX activation.

The authors show (2) that HMGB1 interacts with ATM in NRCMs and suggest that this interaction is an important mechanism to prevent ATM phosphorylation in response to Ang II and subsequent activation of the hypertrophic pathways ERK1/2 and nuclear factor-κB. Future experiments will be required to address whether this interaction also occurs *in vivo*. Moreover, the study shows that ATM activation and activity is not exclusively dependent on HMGB1 because a synergistic cardioprotective effect is observed in HMGB1-Tg animals treated with both Ang II and the ATM inhibitor KU55933, confirming recently published evidence that pharmacologic inhibition of ATM prevents detrimental cardiac remodeling (9).

Overall, some open questions remain. First, persistent DDR promotes cardiac inflammation (8), and it needs to be addressed whether nuclear HMGB1 modulates Ang II–induced inflammatory cells recruitment and cytokines levels *in vivo* or NRCM acquisition of an inflammatory phenotype *in vitro*. Of note, previous studies have not characterized the inflammatory response of HMGB1-Tg animals to a cardiac insult (16–18). Second, the cross-talk between nuclear and extracellular activities of HMGB1 is still unexplored. Although Takahashi et al. (2) did not measure circulating HMGB1 in wild-type and HMGB1-Tg mice or in the supernatant of NRCMs after Ang II treatment, it is likely that the protein is present in the extracellular environment because hypertrophic stimuli are known to induce acetylation and nuclear translocation of HMGB1 in cardiomyocytes (16). Third, it will be important to assess whether extracellular HMGB1 induces DNA damage accumulation or DDR exacerbation, thereby contributing to heart remodeling. Last, nuclear HMGB1 affects the DNA damage repair machinery by modulating the interactions between repair enzymes and damaged DNA (12). Hence, it will be interesting to consider whether, in addition to targeting and inhibiting ATM, nuclear HMGB1 directly protects the DNA from the damage induced by detrimental hypertrophic stimuli.

Regardless of the aforementioned limitations, the study by Takahashi et al. (2) provides novel insights into the mechanism whereby nuclear HMGB1 safeguards the heart from pathological remodeling and supports recent findings that suppression of aberrant DDR may became a novel therapeutic strategy against HF development and progression. Thus, understanding how cardiomyocytes may preserve nuclear HMGB1 to sustain efficient DDR after a cardiac insult represents a potentially clinically relevant therapeutic challenge.

ADDRESS FOR CORRESPONDENCE: Dr. Maurizio C. Capogrossi, Division of Cardiology, Johns Hopkins Bayview Medical Center, 4940 Eastern Avenue, Baltimore, Maryland 21224. E-mail: mcapogr1@jhu.edu.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 4, NO. 2, 2019
APRIL 2019:248–50

REFERENCES

1. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin 2012;8:143–64.

2. Takahashi T, Shishido T, Kinoshita D, et al. Cardiac nuclear high-mobility group box 1 ameliorates pathological cardiac hypertrophy by inhibiting DNA damage response. J Am Coll Cardiol Basic Trans Science 2019;4:234–47.

3. Branzei D, Foiani M. Regulation of DNA repair throughout the cell cycle. Nat Rev Mol Cell Biol 2008;9:297–308.

4. Shiloh Y, Ziv Y. The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. Nat Rev Mol Cell Biol 2013;14:197–210.

5. Sulli G, Di Micco R, d'Adda di Fagagna F. Crosstalk between chromatin state and DNA damage response in cellular senescence and cancer. Nat Rev Cancer 2012;12:709–20.

6. Shukla PC, Singh KK, Quan A, et al. BRCA1 is an essential regulator of heart function and survival following myocardial infarction. Nature Communications 2011;2:593.

7. Siggens L, Figg N, Bennett M, Foo R. Nutrient deprivation regulates DNA damage repair in cardiomyocytes via loss of the base-excision repair enzyme OGG1. FASEB J 2012;26:2117–24.

8. Higo T, Naito AT, Sumida T, et al. DNA single-strand break-induced DNA damage response causes heart failure. Nature Comm 2017;8:15104.

9. Nakada Y, Nhi Nguyen NU, Xiao F, et al. DNA damage response mediates pressure overload-induced cardiomyocyte hypertrophy. Circulation 2019;139:1237–9.

10. Bianchi ME, Agresti A. HMG proteins: dynamic players in gene regulation and differentiation. Curr Opin Genet Dev 2005;15:496–506.

11. Celona B, Weiner A, Di Felice F, et al. Substantial histone reduction modulates genomewide nucleosomal occupancy and global transcriptional output. PLoS Biol 2011;9:e1001086.

12. Liu Y, Prasad R, Wilson SH. HMGB1: roles in base excision repair and related function. Biochim Biophys Acta 2010;1799:119–30.

13. Raucci A, Di Maggio S, Scavello F, D'Ambrosio A, Bianchi ME, Capogrossi MC. The Janus face of HMGB1 in heart disease: a necessary update. Cell Mol Life Sci 2019;76:211–29.

14. Di Maggio S, Milano G, De Marchis F, et al. Non-oxidizable HMGB1 induces cardiac fibroblasts migration via CXCR4 in a CXCL12-independent manner and worsens tissue remodeling after myocardial infarction. Biochim Biophys Acta Mol Basis Dis 2017;1863:2693–704.

15. Limana F, Germani A, Zacheo A, et al. Exogenous high-mobility group box 1 protein induces myocardial regeneration after infarction via enhanced cardiac C-kit+ cell proliferation and differentiation. Circ Res 2005;97:e73–83.

16. Funayama A, Shishido T, Netsu S, et al. Cardiac nuclear high mobility group box 1 prevents the development of cardiac hypertrophy and heart failure. Cardiovasc Res 2013;99:657–64.

17. Kitahara T, Takeishi Y, Harada M, et al. High-mobility group box 1 restores cardiac function after myocardial infarction in transgenic mice. Cardiovasc Res 2008;80:40–6.

18. Narumi T, Shishido T, Otaki Y, et al. High-mobility group box 1-mediated heat shock protein beta 1 expression attenuates mitochondrial dysfunction and apoptosis. J Mol Cell Cardiol 2015;82:1–12.

KEY WORDS cardiac hypertrophy, DNA damage, heart failure, HMGB1