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MicroRNAs as pathophysiological targets: An emerging nexus for personalized medicine in heart failure?

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Heart failure (HF) remains a major driver of morbidity, mortality, and health care expenditures in the US and underlies the number one reason for hospitalization in adults >65 years of age in the United States [1]. Over 650,000 new HF cases are diagnosed annually and over 5 million adults in the United States (and 23 million worldwide) carry a clinically active diagnosis of HF [2]. With an estimated 1 in 5 adults reaching >65 years of age by 2050, the number of adults afflicted by HF is predicted to rapidly rise. While significant progress in medical and device therapies have contributed to improvements in quality of life and survival over the past few decades, the absolute mortality rates for HF remain frustratingly high at approximately 50% within 5 years of diagnosis [1]. Current therapeutic decision making is largely based on similar clinical manifestations of HF [e.g., dyspnea, peripheral edema, cool/wet, warm/dry, reduced (HF-rEF), or preserved left ventricular ejection fraction (HF-PEF)]. However, as a heterogeneous disease with a range of predisposing clinical risk factors as well as environmental and genetic components, the specific etiologies and pathophysiological events underlying each case of HF are likely to offer better targets, prognosis, and therapeutic opportunities than the “one-size-fits-all” approach. Indeed, personalized medicine has emerged as a cornerstone for modern day oncologic therapeutics and appears to underlie susceptibility and resistance to drug therapy through a careful understanding of genome–phenome relationships. Analogous to the field of cancer, HF offers a range of opportunities to strengthen genome–phenome interactions that may provide pathophysiological insights and new therapeutic targets. Intense scientific interest pre-clinically has focused on identifying common pathophysiological events, molecular signaling pathways, and cellular paradigms that may discriminate phenotypically similar HF. These findings have lagged behind on the translational level for human HF patients. While the lack of accessible tissue is one of the common obstacles cited for lack of progress in HF, there is an abundance of accessible blood or plasma. Furthermore, accumulating experimental and clinical studies have linked focused pathophysiological events in a range of HF subtypes (e.g., myocardial infarction, hypertrophic, valvular, and inflammatory) to dynamic changes in circulating biomarkers. It is in this context that microRNAs may provide a critical nexus in HF bridging pathophysiological events to diagnosis, prognosis, and targeted therapeutics.

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microRNAs, small single-stranded, evolutionarily conserved RNAs derived from the ~98% of the non-coding genome, regulate gene expression on the post-transcriptional level by mRNA degradation or translational repression and actively contribute to key pathophysiological events in HF, as highlighted in this issue of the Journal [3]. In this review, the authors provide a focused update on the identification and functional relevance of miRNAs involved in specific aspects of HF including fibrosis, angiogenesis, hypertrophy and metabolic balance, and inflammation. While approximately 2500 human mature microRNA have been identified to date, only a handful of miRNAs have been implicated in these pathophysiological HF events. Furthermore, many of these miRNAs are detectable as circulating biomarkers in plasma, thereby linking key molecular events as potential biomarkers and therapeutic targets in specific HF subsets.

For example, one of the hallmarks of adverse cardiac remodeling is the development of excessive replacement fibrosis, an effect due to in part to enhanced extracellular matrix deposition by cardiac fibroblasts [4]. Indeed, positive LV remodeling with reduced interstitial fibrosis is one of the major benefits from use of angiotensin converting enzyme inhibitors in patients post-MI with reduced ejection fraction [5]. Among miRNAs expressed in cardiac fibroblasts, miR-29 has emerged as a potential target for LV remodeling. Several miR-29 family members are reduced in the ischemic border-zone area after MI. Neutralization of miR-29 expression induced fibrosis in vivo by de-repression of its target genes including COL1A1, COL1A2, and COL3A1 [6]. Another study recently linked miR-29 uniquely to both hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy [7]. Consistent with these studies, miR-29 family members are also reduced in response to other stimuli associated with fibrosis such as pressure overload and chronic calcineurin signaling [8]. A different cardiac-enriched miRNA, miR-133, regulates cardiac fibrosis by targeting connective tissue growth factor (CTGF), and TGF- β 1 receptor [9,10], key regulators of organ fibrosis. Consistently, miR-133-deficient mice exhibit heart failure with severe cardiac fibrosis and apoptosis [10]. Finally, miR-101a and miR-29 are both highly expressed in cardiac fibroblasts. While the functional role of miR-29 in regulating fibrosis remains controversial (likely due to different anti-miR chemistries and disease models examined), miR-101a overexpression in infarcted hearts improved cardiac function in part by decreasing cardiac fibrosis and reducing expression of its target c-FOS and, in turn, TGF- β 1 signaling [11]. Collectively, these studies reveal that manipulation of a cassette of miRNAs may be useful for suppressing cardiac fibrosis, a major pathological process that typically leads to LV non-compliance, arrhythmias, and heart failure.

The induction and orchestration of new blood vessels is critical for tissue repair in response to injury in ischemic cardiovascular disease such as myocardial infarction (MI) or in response to pressure overload such as pathological cardiac hypertrophy. As highlighted in the review by Duygu et al. [3], several notable miRNAs have been identified that serve as either pro- or anti-angiogenic regulators of neovascularization and cardiac repair. For example, inhibition of anti-angiogenic miRNAs, such as miR-92a, miR-24, miR-34, and miR-26a, can each markedly improve cardiac function by promoting myocardial angiogenesis and regulating distinct targets and signaling pathways [12–15]. In contrast, pro-angiogenic miRNAs, such as miR-126 and miR-210 [16,17], are protective for myocardial function by regulating key angiogenic events such as endothelial sprouting or

capillary formation. The time for induction of myocardial angiogenesis may be more important for specific inducers of heart failure. For example, earlier angiogenesis may be beneficial for MI-induced heart failure. Indeed, neutralization of miR-26a markedly induced angiogenesis ~2-fold within 2-days of LAD ligation that significantly improved LV function [15,18]. In contrast, a more gradual induction of myocardial angiogenesis may be useful for pathological hypertrophic states in which cardiomyocyte hypertrophy slowly outstrips capillary density, an effect leading to myocardial ischemia and eventually HF. Taken together, phase-specific therapeutic targeting of miRNAs may be considered depending on the underlying etiology and how advanced HF manifests. For many miRNA studies, it remains unclear whether, for example, late induction of angiogenesis, particularly in aged subjects, will be truly beneficial for repair.

The induction and orchestration of new blood vessels is critical for tissue repair in response to injury in ischemic cardiovascular disease such as myocardial infarction (MI) or in response to pressure overload such as pathological cardiac hypertrophy. As highlighted in the review by Duygu et al. [3], a relatively large number of miRNAs have been identified as either pro-hypertrophic (e.g., miR-199, miR-214, miR-208, miR-212/miR-132, and miR-23a) or anti-hypertrophic (e.g., miR-1, miR-133, and miR-378), whereas others such as miR-25 may exhibit both pro- or anti-hypertrophic properties depending in part upon use of different models. Among the pro-hypertrophic miRNAs, miR-199b may hold therapeutic interest for its potent ability to regulate the NFAT signaling pathway known for mediating adverse cardiac hypertrophy. miR-199b expression increases in mouse and human HF. Indeed, neutralization of miR-199b during pressure overload in mice abrogated the onset of HF and even reversed LVH and fibrosis, an effect due to regulating Dyrk1a and in turn phosphorylation of NFAT factors [19]. Cardiac metabolic switching is also an important event in response to pathological hypertrophic stimuli. miR-214, which belongs to the miR-199a cluster, has been shown to control the balance of mitochondrial fatty acid oxidation and glucose metabolism by regulating the target gene PPAR β . Indeed, antagonism of miR-214 in cardiac pressure overload in mice restored mitochondrial fatty acid oxidation and improved LV remodeling and function [20]. miR-133 and miR-1 are also encoded within the same cluster. Inhibition of miR-133 uniquely induces spontaneous cardiac hypertrophy, whereas miR-133 overexpression improved LV function after chronic pressure overload, an effect mediated by targeting the β 1AR signaling pathway including β 1AR itself [21]. Similarly, miR-1 overexpression attenuated isoproterenol-induced cardiac hypertrophy [22]. Finally, significant interest exists for miR-208a and miR-208b, encoded by their respective intronic regions of the α -MHC and β -MHC genes, as potential therapeutic targets. Inhibition of miR-208a during pressure overload prevents myosin α - to β -switching and improves LV function and survival in mice [23]. Because miR-208 can be readily identified in peripheral blood, saliva, and urine, this miRNA may represent an important link between cardiac hypertrophy and prognosis and management of HF in patients.

Cardiac inflammation contributes significantly to LV remodeling and repair in a range of pathologies such as acute or chronic myocarditis, autoimmune diseases, LV hypertrophy, or during the early phases of myocardial injury post-MI. Excessive pro-inflammatory macrophage recruitment and activation in the heart may be deleterious to cardiac repair. For example, neutralization of miR-155 in leukocytes significantly reduced cardiac

inflammation, LV hypertrophy, and HF in mice due to its targeting suppressor cytokine signaling 1 gene (Socs1) in macrophages [24]. The role of miRNA-mediated control of inflammation of other relevant leukocyte subsets and non-cardiomyocyte cell types such as endothelial cells and fibroblasts remain to be fully elucidated in HF.

Taken together, these miRNA studies raise a number of challenges and opportunities in the diagnosis, prognosis, and personalized management of heart failure therapies. First, it raises the proposition that diverse etiologies of heart failure elicit key microRNAs necessary for regulating pathophysiological events including cardiac fibrosis, angiogenesis, hypertrophy, and inflammation. Second, therapeutic manipulation of their expression may allow for fine-tuning of specific cardiac reparative responses in HF. Third, because these miRNAs are detectable in circulating plasma (including in saliva and urine for a few studies that examined this), they may serve as a more precise HF subgroup categorization to facilitate prognosis and therapeutic decision-making than the current standards of “HF-rEF” or “HF-PEF” which do not currently define pathophysiological insights. Fourth, the role of extracellular miRNA communication, such as miRNA secretion into microparticles, apoptotic bodies, or RNA-binding proteins, requires further clarity for therapeutic targeting and detection. Fifth, consideration of microRNA-based therapeutics in HF should carefully evaluate potential off-target effects in other cells or tissues; consequently, those miRNAs expressed uniquely in specific cell types or tissues may possess more favorable properties for targeting. While targeting a single miRNA may in theory alter several targets and signaling pathways, experimental and clinical experience to date is reassuring, including a phase II trial for anti-miR-122 in hepatitis C infection [25], that have demonstrated durable effects without adverse side effects. Sixth, the role of miRNAs in other important pathophysiological cardiac events in response to injury including cardiac apoptosis, necrosis, and progenitor/stem cells used for tissue regeneration require further clarity. Finally, while the roles of miRNAs in stage-specific pathophysiological HF events are well-defined from an abundance of pre-clinical studies, their expression and potential roles in human subjects with HF has been minimally examined, especially from a prognostic perspective. Further exploration of HF-associated miRNAs, and other non-coding RNAs, in longitudinal clinical studies may allow us to establish miRNAs as a nexus for personalization in HF by bridging pathophysiological events, prognosis, and stage-specific therapy.

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References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013; 128:e240–327. [PubMed: 23741058]
2. McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heart failure: public and private health burden. *Eur Heart J*. 1998; (Suppl. 19):9–16.
3. Duygu B, de Windt LJ, da Costa Martins PA. Targeting microRNAs in Heart Failure. *Trends Cardiovasc Med*. 2015; 26:99–110. [PubMed: 26119078]

4. Palardy M, Ducharme A, O'Meara E. Inhibiting the renin-angiotensin system with ACE Inhibitors or ARBs after MI. *Curr Heart Fail Rep*. 2007; 4:190–7. [PubMed: 18221615]
5. Vaughan DE, Pfeffer MA. Post-myocardial infarction ventricular remodeling: animal and human studies. *Cardiovasc Drugs Ther*. 1994; 8:453–60. [PubMed: 7947361]
6. van Rooij E, Sutherland LB, Thatcher JE, DiMaio JM, Naseem RH, Marshall WS, et al. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. *Proc Natl Acad Sci U S A*. 2008; 105:13027–32. [PubMed: 18723672]
7. Roncarati R, Viviani Anselmi C, Losi MA, Papa L, Cavarretta E, Da Costa Martins P, et al. Circulating miR-29a, among other up-regulated microRNAs, is the only biomarker for both hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2014; 63:920–7. [PubMed: 24161319]
8. van Rooij E, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. *Proc Natl Acad Sci U S A*. 2006; 103:18255–60. [PubMed: 17108080]
9. Duisters RF, Tijssen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, et al. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ Res*. 2009; 104:170–8. [176p following 178]. [PubMed: 19096030]
10. Liu N, Bezprozvannaya S, Williams AH, Qi X, Richardson JA, Bassel-Duby R, et al. microRNA-133a regulates cardiomyocyte proliferation and suppresses smooth muscle gene expression in the heart. *Genes Dev*. 2008; 22:3242–54. [PubMed: 19015276]
11. Pan Z, Sun X, Shan H, Wang N, Wang J, Ren J, et al. MicroRNA-101 inhibited postinfarct cardiac fibrosis and improved left ventricular compliance via the FBJ osteosarcoma oncogene/transforming growth factor-beta1 pathway. *Circulation*. 2012; 126:840–50. [PubMed: 22811578]
12. Bonauer A, Carmona G, Iwasaki M, Mione M, Koyanagi M, Fischer A, et al. MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. *Science*. 2009; 324:1710–3. [PubMed: 19460962]
13. Boon RA, Iekushi K, Lechner S, Seeger T, Fischer A, Heydt S, et al. MicroRNA-34a regulates cardiac ageing and function. *Nature*. 2013; 495:107–10. [PubMed: 23426265]
14. Fiedler J, Jazbutyte V, Kirchmaier BC, Gupta SK, Lorenzen J, Hartmann D, et al. MicroRNA-24 regulates vascularity after myocardial infarction. *Circulation*. 2011; 124:720–30. [PubMed: 21788589]
15. Icli B, Wara AK, Moslehi J, Sun X, Plovie E, Cahill M, et al. MicroRNA-26a regulates pathological and physiological angiogenesis by targeting BMP/SMAD1 signaling. *Circ Res*. 2013; 113:1231–41. [PubMed: 24047927]
16. Hu S, Huang M, Li Z, Jia F, Ghosh Z, Lijkwan MA, et al. MicroRNA-210 as a novel therapy for treatment of ischemic heart disease. *Circulation*. 2010; 122:S124–31. [PubMed: 20837903]
17. Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, et al. The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. *Dev Cell*. 2008; 15:261–71. [PubMed: 18694565]
18. Icli B, Dorbala P, Feinberg MW. An emerging role for the miR-26 family in cardiovascular disease. *Trends Cardiovasc Med*. 2014; 24:241–8. [PubMed: 25066487]
19. da Costa Martins PA, Salic K, Gladka MM, Armand AS, Leptidis S, el Azzouzi H, et al. MicroRNA-199b targets the nuclear kinase Dyrk1a in an auto-amplification loop promoting calcineurin/NFAT signalling. *Nat Cell Biol*. 12:1220–7.
20. el Azzouzi H, Leptidis S, Dirx E, Hoeks J, van Bree B, Brand K, et al. The hypoxia-inducible microRNA cluster miR-199a approximately 214 targets myocardial PPARdelta and impairs mitochondrial fatty acid oxidation. *Cell Metab*. 2013; 18:341–54. [PubMed: 24011070]
21. Castaldi A, Zaglia T, Di Mauro V, Carullo P, Viggiani G, Borile G, et al. MicroRNA-133 modulates the beta1-adrenergic receptor transduction cascade. *Circ Res*. 2014; 115:273–83. [PubMed: 24807785]
22. Ikeda S, He A, Kong SW, Lu J, Bejar R, Bodyak N, et al. MicroRNA-1 negatively regulates expression of the hypertrophy-associated calmodulin and Mef2a genes. *Mol Cell Biol*. 2009; 29:2193–204. [PubMed: 19188439]

23. Montgomery RL, Hullinger TG, Semus HM, Dickinson BA, Seto AG, Lynch JM, et al. Therapeutic inhibition of miR-208a improves cardiac function and survival during heart failure. *Circulation*. 2011; 124:1537–47. [PubMed: 21900086]
24. Heymans S, Corsten MF, Verhesen W, Carai P, van Leeuwen RE, Custers K, et al. Macrophage microRNA-155 promotes cardiac hypertrophy and failure. *Circulation*. 2013; 128:1420–32. [PubMed: 23956210]
25. Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, et al. Treatment of HCV infection by targeting microRNA. *N Engl J Med*. 2013; 368:1685–94. [PubMed: 23534542]