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REVIEW

Using Omics to Identify Novel Therapeutic Targets in Heart Failure

Christelle Lteif, PharmD, PhD; Yimei Huang, PharmD; Leonardo A. Guerra, BS; Brian E. Gawronski, PharmD; Julio D. Duarte, PharmD, PhD

ABSTRACT: Omics refers to the measurement and analysis of the totality of molecules or biological processes involved within an organism. Examples of omics data include genomics, transcriptomics, epigenomics, proteomics, metabolomics, and more. In this review, we present the available literature reporting omics data on heart failure that can inform the development of novel treatments or innovative treatment strategies for this disease. This includes polygenic risk scores to improve prediction of genomic data and the potential of multiomics to more efficiently identify potential treatment targets for further study. We also discuss the limitations of omic analyses and the barriers that must be overcome to maximize the utility of these types of studies. Finally, we address the current state of the field and future opportunities for using multiomics to better personalize heart failure treatment strategies.

Key Words: drug discovery ■ genomics ■ heart failure ■ multiomics ■ polygenic risk score ■ therapeutics ■ transcriptomics

The study of various omics in biomedical research has expanded over the past 20 years. Constant evolvement in technologies related to next-generation sequencing, global proteomics, and multiomic integration have allowed a more specific knowledge of disease pathology at the molecular level, thus leading to more targeted drug development. The suffix "-omics" refers to the study of the totality of molecules or biological processes involved within an organism with different omics involving different constituents such as the study of DNA variation in a cell or organism with genomics, or the study of the complete set of RNA transcripts present in a cell or tissue with transcriptomics. The field has now expanded to also include epigenomics, proteomics, metabolomics, and more. Individually, omics analyses can provide novel insights unconstrained by prior biological knowledge or a mechanism-based hypothesis because all potential candidates are analyzed. When multiomics data types are combined, they become even more powerful tools for understanding biological processes and disease development pathways.

Comprehensive omics methods have the ability to provide significant insight into a heterogeneous disease such as heart failure (HF), where multiple etiologies can occur and several biological processes are involved. Such a level of understanding can be an important tool for the identification of novel therapeutic targets for future development into new HF medications and other treatment modalities (Figure). Despite the addition of several treatment options for heart failure with reduced ejection fraction (HFrEF) over the past 10 years, mortality rates do not seem to have drastically changed.[1] Moreover, novel treatment targets are especially needed for HF types where few treatments have been shown to reduce mortality, such as heart failure with preserved ejection fraction (HFpEF). Thus, the goal of this article is to discuss the literature surrounding omics research in HF that may be relevant to inform novel treatment strategies and to identify opportunities for future research in the field.

GENOMICS

The goal of a genome-wide association study (GWAS) is to identify polymorphisms strongly associated with a clinical phenotype, such as disease risk, from across the

Correspondence to: Julio D. Duarte, PharmD, PhD, Center for Pharmacogenomics and Precision Medicine, Department of Pharmacotherapy and Translational Research, University of Florida College of Pharmacy, HSC PO Box 100486, Gainesville, FL 32610. Email juliod@cop.ufl.edu
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Nonstandard Abbreviations and Acronyms

AI	artificial intelligence
BET	bromodomain and extraterminal
CAD	coronary artery disease
DCM	dilated cardiomyopathy
GWAS	genome-wide association study
HERMES	Heart Failure Molecular Epidemiology for Therapeutic Targets
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HOMAGE	Heart Omics in Ageing
ICM	ischemic cardiomyopathy
ID	inhibitor of DNA binding
LTA_4H	leukotriene A4 hydrolase
LV	left ventricle
MI	myocardial infarction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PRP	polygenic response predictor
PRS	polygenic risk scores
SGLT2	sodium-glucose cotransporter-2
SVEP1	Sushi, von Willebrand factor type A, EGF, and pentraxin domain containing 1
TGF-β/BMP	transforming growth factor-β/bone morphogenetic protein
TMAO	trimethylamine-N-oxide
UCHL1	ubiquitin C-terminal hydrolase L1
VEGF	vascular endothelial growth factor

genome at the population level.[2] Most GWASs in HF populations used HF incidence or surrogate traits (such as echocardiographic measures or biomarker levels) as the primary phenotype for analysis, while few have assessed clinical end points such as HF hospitalization or mortality.[3–10] HF incidence-associated loci may inform therapeutic targets to prevent disease occurrence, whereas end point-associated loci may better inform targets to halt disease progression.

Since the first GWAS publication of HF incidence in 2007,[3] 16 loci have been significantly linked to this phenotype.[4,5] Some of these genomic effects on HF incidence seem to be mediated entirely or partially by risk factors for HF, such as atrial fibrillation, coronary artery disease (CAD), and body mass index.[4] Most studies using HF development as a binary outcome were underpowered to detect clinically significant effects. Efforts to overcome this limitation included meta-analysis of multiple GWASs in large consortia or using quantitative surrogate traits as GWAS phenotypes.[4,5,11] Adopting the former approach, the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium conducted the largest meta-analysis of HF GWASs to date.[4] The consortium identified 11 loci, of which 10 were novel, constituting the majority of the HF incidence-associated genomic loci to date. These loci had previously reported associations with various types of cardiomyopathy, cardiovascular risk factors (eg, low-density lipoprotein cholesterol, CAD, myocardial infarction [MI], atrial fibrillation, and obesity), and cellular processes such as cardiac repair and selective autophagy under stress or injury.[4]

The latter approach, using surrogate traits as the primary GWAS phenotype, such as left ventricular (LV) structure and functional parameters, echocardiographic parameters, or serum biomarker levels (such as B-type natriuretic peptide or cardiac troponin T), makes up most of the HF GWAS literature. Over a 100 loci and genes have been associated with these surrogate traits.[5,12] Representative genes included *SLC35F* (associated with LV diastolic function),[13] *MYH6* (associated with heart rate),[14,15] and *SCN10A* (associated with various forms of arrhythmia).[15,16] These loci are thought to either reflect the LV contractile regulation mechanism (eg, LV hypertrophy, LV remodeling, or volume overload), regulate cardiac development pathways (eg, mammalian target of rapamycin pathway, cytoskeletal signaling pathway), or confirm the interplay between HF and its risk factors (eg, hypertension, CAD, arrhythmia, and obesity).[5,12] Some of these GWASs have implicated emerging biomarkers involved in HF biology, such as suppression of tumorgenicity 2, galectin-3, and telomere length.[5] Many of these emerging biomarkers' associations with HF have been validated through multiple protein association studies.[17–20] In addition, the single-nucleotide polymorphisms associated with protein levels can be selected as protein quantitative trait loci to construct the instrumental variable in Mendelian randomization, which can elucidate the causal role of those proteins in HF (see Proteomics section). Of these identified potential targets, the sodium channel SCN10A was specifically blocked with the small-molecule A-803467 in mouse and rabbit cardiomyocytes, leading to antiarrhythmic effects.[21] These antiarrhythmic effects were not observed in cardiac myocytes from *Scn10a* knockout mice, suggesting that the antiarrhythmic effect is very specific to SCN10A receptor blocking.[21] While associations implicated in GWAS studies have the potential to lead to druggable targets with disease improvement benefits, further research is needed before these emerging biomarkers can be leveraged to drive diagnostic and therapeutic advances in HF.

Another challenge for HF genomics studies lies in the heterogeneous nature of the disease. Likely due to this challenge as well as the publication bias toward studies reporting significant associations, few GWASs have been published assessing the critical clinical end points of

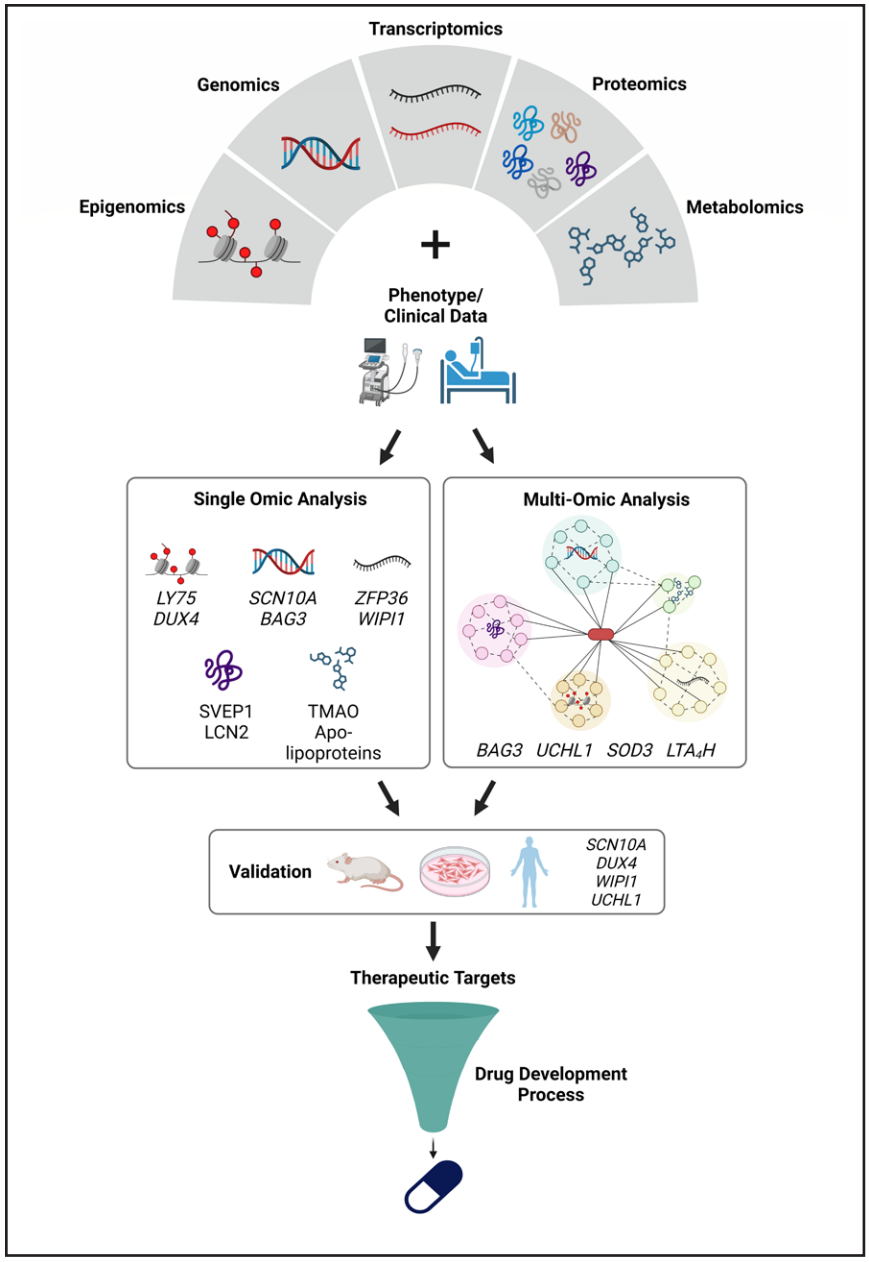

Figure. Applying and integrating omics methods for the development of novel therapies for heart failure. The different types of omics that have been conducted in heart failure include epigenomics, genomics, transcriptomic proteomics, and metabolomics. Combined with phenotype/clinical data, omics can be analyzed individually or combined using a multiomic strategy. Examples of genes/moieties stemming from the different omics analyses conducted in HF populations are listed. Some associations identified through the omics analyses were validated in vitro or in vivo and show potential as potential therapeutic targets to be further investigated, with the ultimate goal being novel therapeutic development. Created with BioRender.com.

HF hospitalization and mortality. The existing 3 GWASs that assessed mortality in patients with HF discovered 1 significantly associated locus each. However, some of these earlier findings did not reach the now standardly used genome-wide significance threshold ($P=5\times10^{-8}$),[8] and the associations were not clearly validated.[7,8,10] In addition, most of these studies predominantly focused on participants of European descent, limiting their generalizability to other ancestries. A more recent GWAS identified associations between variants in *FGD5* and an increased risk of all-cause mortality or rehospitalization in patients with acute decompensated HF.[10] *FGD5* encodes a regulator protein in the vascular endothelial growth factor (VEGF) pathway-mediated vasodilation, and the genetic effect was shown to be independent of CAD history. Because this locus has not been linked to mortality or hospitalization in chronic HF, it is unclear whether it represents a distinct pathophysiology of acute decompensated HF that differs from chronic, stable HF.

Although the discovery of genetic variants associated with HF development or progression is valuable in identifying a gene or pathway, a complex disorder such as HF may require the assessment of a combined set of variants and genes to improve our understanding of the underlying mechanisms in HF. Polygenic risk scores (PRS), also referred to as genetic risk scores, may be a useful tool to account for multifactorial genetic risk observed in complex disorders such as HF. These scores capture the small impact of individual variants by summing the weighted contribution of each individual variant.[22]

A predictive PRS developed from the significant and validated loci (*HSPB7*, *TTN*, *BAG3*, *MTSS1*, *ALPK3*, *GRK5*, *NMB*, and *MMP11*) previously associated with LV measures, such as end-diastolic volume, ejection fraction, and LV mass, demonstrated a higher risk of HF development when comparing the bottom quintile to the top quintile of the PRS.[12] Additionally, a prognostic PRS comprised 69 variants outperformed a clinical risk score in predicting 1-year mortality in a cohort of patients with HFpEF.[23] Patients in the highest PRS risk tertile had a 30-fold increased risk of 1-year mortality compared with those in the lowest tertile. While the promise remains to be seen, PRS may improve our understanding of the key biological pathways involved in HF development and progression, providing another method to identify potential therapeutic targets implicated in HF. As methods improve with optimized predictive models through machine learning and power increases with larger database sizes, novel therapeutic targets for HF may be identified through PRS.

Polygenic scores have also been utilized to predict response to HF therapy. Lanfear et al[24] derived a validated polygenic response predictor (PRP) for beta blocker survival benefit in the treatment of patients with HFrEF. Beta blocker exposure was associated with improved survival in patients who were PRP-predicted responders, while beta blockers showed no association with survival in PRP-predicted nonresponders. This PRP was also validated in the UK Biobank in a cohort of 7141 patients of European ancestry, where patients who were PRP-predicted responders also showed survival benefits associated with beta blocker dosage.[25] This example of polygenic score development demonstrates the potential of using this method to identify specific populations that might benefit from a therapeutic agent. Through the identification of pathways involved in the development or progression of HF and precision targeting of therapeutics, PRS may provide the opportunity to develop precision medicines during the drug development process.

EPIGENOMICS

Epigenomics includes the analysis of epigenetic interactions, including DNA methylation and histone modifications. Thus far, DNA methylation has been a primary focus within epigenomic HF research. The methylome encompasses the total methylation across the genome and can play a pivotal role in influencing gene expression and biological processes relevant to HF progression.[26] While DNA methylation is relatively stable depending on the tissue, it remains susceptible to alterations induced by environmental factors.[27]

Abnormal patterns of DNA methylation seem to be involved in maladaptive cardiac remodeling, including ischemia, inflammation, hypertrophy, and fibrosis.[28] In 1 study, DNA methylation profiles were analyzed in LV tissue samples obtained from patients with dilated cardiomyopathy (DCM) and controls without HF.[29] The investigators observed hypermethylation of a CpG island near the promoter of *LY75* (the gene encoding lymphocyte antigen 75) and hypomethylation within the CpG island of *ADORA2A* (encoding adenosine receptor A2A) in the DCM group, which corresponded with a significant reduction in expression of these 2 genes. The investigators also showed that knockdown of these 2 genes through Morpholino-modified antisense oligonucleotides resulted in the development of HF in a zebrafish model. In a separate study comparing patients with end-stage HF with those with nonfailing hearts, researchers observed differential DNA methylation patterns in CpG islands near gene promoters, intragenic CpG islands, and within gene bodies.[30] Notably, they observed reduced global gene promoter methylation correlating with upregulated, but not downregulated, genes in cardiomyopathy. This suggests that differential DNA methylation in crucial regions may contribute to overexpression of genes that are involved in the development and progression of HF, providing a possible new strategy for controlling the expression of key HF genes. As for intragenic sites, hypermethylation of *DUX4* correlated with its downregulation in end-stage cardiomyopathic hearts compared with control, and siRNA knockdown of this locus in HL1 mouse atrial cardiomyocyte cells resulted in reduced cell viability, providing a specific site to be further studied and validated.[30]

DNA methylation patterns not only coexist with underlying disease processes but also correlate with other cardiac alterations that potentially contribute to the final cardiac phenotype of HF.[31] However, many DNA methylation studies have limited sample sizes, which can affect the statistical power and generalizability of their findings.[26,29,30] While the dynamic nature of DNA methylation can provide insight on the regulation of gene expression, it poses challenges in interpreting context because methylation can undergo changes over time due to various factors, including environmental influences and aging.[27] Lastly, DNA methylation exhibits tissue-specific variations and is not uniform within the genome's CpG sites.[32] Thus, focusing solely on global methylation levels may disregard site-specific changes that could have significant functional implications.

DNA methyltransferases play a crucial role in mediating DNA methylation throughout the genome and represent the next most-studied epigenetic processes in HF.[33] Although DNA methyltransferase inhibitors are not widely used in cardiovascular therapeutics, the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin has been shown to prevent DNA methylation, indicating its potential role in gene silencing and offering insight into a potential mechanism by which SGLT2 inhibitors can exert benefits in patients with HF.[34,35] In myocardial tissue from a mouse model of cardiac remodeling, the

DNA methylation inhibitor 5-azacytidine (at a lower dose than used in cancer) attenuated DNA methylation and DNA methyltransferase 1 expression increases.[36] This reduction in global DNA methylation was also paralleled by reduced myocardial hypertrophy and fibrosis.

Histone modifications also influence epigenomics, regulating chromatin configuration and thus accessibility to transcription factors. While there are no current Food and Drug Administration–approved HF therapeutics targeting epigenetic modifications directly, the histone deacetylase inhibitors givinostat and apicidin derivative have shown promising early results by reducing cardiac fibrosis and hypertrophy, respectively.[37,38] In another study, genome-wide histone acetylation changes were mapped using a mouse model of hypertrophy that was treated with histone deacetylase trichostatin A.[39] Trichostatin A attenuated cardiac hypertrophy through histone deacetylation of nuclear factor-kappa target genes involved in inflammation as well as genes involved in cardiac contraction. Histone deacetylase inhibition with vorinostat has also been shown to reduce LV hypertrophy and improve diastolic and pulmonary functions in a feline HFpEF model.[40] Another component of histone modification that appears to have an emerging role in HF is the BET (bromodomain and extraterminal) family of proteins that recognize acetylation marks and modulate transcription factors. BET proteins have exhibited increased expression in cardiac hypertrophy.[40] An inhibitor of BET acetyl-lysine reader proteins appears to reduce cardiomyocyte hypertrophy in vitro and both LV hypertrophy and fibrosis in mouse models of HF.[41,42] In addition, the BET inhibitor apabetalone decreased first-hospitalizations for HF, total HF hospitalizations, and the composite of cardiovascular death or HF hospitalization in a clinical trial of patients with diabetes and acute coronary syndrome.[43]

Because of the epigenome's ability to respond to the environment, identifying consistent epigenomic signatures can be challenging. Analyses can be confounded by patient comorbidities, medications, and blood cell composition, which can vary in the setting of inflammation (which can be present in heart disease). When these factors can be accounted for, epigenomics confers the advantage of incorporating environmental factors as relatively stable DNA modifications that could provide insight into underlying HF mechanisms.

TRANSCRIPTOMICS

Transcriptomic analyses assess changes across the whole transcriptome within specific cells or tissues in relation to a disease or a stimulus. It can include all transcripts, including messenger RNAs (mRNAs), long noncoding RNAs (lncRNAs), and microRNAs (miRNAs). The most common transcriptomics techniques are RNA sequencing (RNAseq) and cDNA microarrays, with RNAseq becoming the predominant technique used in recent years. Transcriptomic profiling provides large quantitative information about gene expression changes to study variations and can identify novel biological gene regulatory networks to be explored using more focused methods. Circulating miRNAs and lncRNAs have been extensively studied as diagnostic tools in cardiovascular diseases, specifically as biomarkers in HF for risk stratification, subtype differentiation, and prognosis.[44] Beyond that, the use of transcriptional profiling to identify potential underlying mechanisms of HF development or progression can provide new insights into potential new therapeutic targets. Transcriptomics from whole tissue samples only capture the total level of expression, failing to distinguish individual cell variations.[45] In contrast, single-cell RNAseq improves our understanding of complex diseases by subtyping cells, identifying novel treatment targets, improving the selection of preclinical disease models, providing better insight into disease mechanisms of action, and improving drug response monitoring.[45]

Transcriptomic analyses have reported differentially expressed genes associated with various pathways such as fibrosis, cardiac muscle contraction, and inflammatory processes in HF.[46] In a multilevel transcriptomic study (mRNAs, miRNAs, and lncRNAs), increased expression of the collagen type I alpha 1 chain (*COL1A1*) gene in heart tissue was associated with HF progression, measured as survival time before transplantation, as well as poor survival within 1 year of heart transplantation from HF.[47] A meta-analysis of RNAseq in mouse and human coronary vascular endothelial cells subjected to ischemic injury identified species-conserved genes involved in neovascularization regulatory pathways.[48] The most significant differentially expressed genes included the post-transcriptional regulator of immune response *ZFP36*—which was shown to regulate endothelial cell proliferation—as well as *VEGF-C*, which promoted vascular regeneration when given in vivo. Multiple gene networks involved in collagen-containing extracellular matrix regulation have been associated with cardiomyopathy as well as HF development and progression, suggesting that targeting these pathways may prevent further progression of HF.[49,50] In a HF mouse model, nintedanib decreased expression of *COL1A1* and *COL3A1* and reduced cardiac fibrosis, but whether this will translate to patients with HF remains unstudied.[51] In the HOMAGE trial (Heart Omics in Ageing), spironolactone had pleiotropic effects in patients at increased risk of developing HF by reducing biomarkers of inflammation (such as IL17A), thrombosis (such as VEGF), and collagen formation (such as COL1A1). No long-term outcomes data were reported related to these effects, but the cardioprotective effects of targeting these biomarkers could prevent the progression to HF and should be studied.[52]

In advanced HF with right ventricular dysfunction, analyzing the ventricular transcriptome showed that increased expression of the beta-transducin repeat domain and phosphoinositide interacting 1 (*WIPI1*) gene was associated with noncanonical autophagy in the failing right ventricle. In addition, small interfering RNA silencing of *Wipi1* in rat ventricular myocytes in vitro restricted noncanonical autophagy and reduced aldosterone-induced mitochondrial superoxide levels.[53] These data suggest that *WIPI1*, known to be implicated in both noncanonical and canonical autophagy pathways, may be a potential therapeutic target in advanced HF. In another study, inflammatory pathways associated with cardiac leukocyte infiltration were upregulated in cardiac nonmyocytes of a western diet–induced diastolic dysfunction mouse model. This infiltration appears independent of cardiac fibrosis, and this inflammatory phenotype was prevented by smooth muscle cell-mineralocorticoid receptor deletion.[54]

A recent large multicenter whole blood transcriptomic study identified differentially expressed genes associated with cardiovascular mortality in patients with HF. These genes belonged to pathways related to T-cell costimulation, positive regulation of T-cell proliferation, proteasome-mediated ubiquitin-dependent protein catabolic process, adaptive immune response, and erythrocyte development.[55] Interestingly, using an in vitro drug signature database revealed that some drugs, previously shown to target HF-related molecular pathways, can also reverse the gene expression patterns of the differentially expressed genes and may be repurposed for HF. A systematic review and meta-analysis of transcriptomic data evaluated the degree of consistency between a large set of RNAseq and microarray studies comparing healthy and end-stage HF tissues and found that structured data integration of large databases was feasible and HF gene signatures may be conserved within the different studies when evaluated together.[56] The gene sets emerging from this study included established transcription factors associated with HF, such as Myocyte Enhancer Factor 2, Natriuretic Peptide A, and the C-X-C Motif Chemokine Ligand 12. However, less explored targets were also revealed, such as Zinc Finger and BTB Domain Containing 7A, One Cut Homeobox 1, and Collagen Type VIII Alpha 1 Chain, associated with fibrotic pathways.

The TGF-β/BMP (transforming growth factor-β/bone morphogenetic protein) signaling pathway was shown to be associated with ischemic cardiomyopathy (ICM) and DCM through an integrated mRNA and miRNA analysis from myocardial samples and was also one of the top pathways associated with cardiac remodeling, HF development, and HF progression when comparing patients with HF to patients with nonfailing hearts.[49,50,57] Genes downstream of the BMP signaling pathway have also been associated with HF progression. Two genes in the inhibitor of DNA binding (*ID*) gene family (*ID1* and *ID2*) were upregulated in an RNAseq analysis of patients with HF who developed severe pulmonary hypertension.[58] This suggests that the *ID* gene family, or potentially other specific genes belonging to TGF-β signaling, may be involved in HF progression, and targeting this pathway may potentially be a viable treatment strategy.

Comparing the myocardial transcriptome among HFpEF, HFrEF, and healthy hearts revealed that pathways related to protein hemostasis, endoplasmic reticulum stress, and angiogenesis were uniquely upregulated in HFpEF, whereas pathways related to fibrosis, hypertrophy, oxidative stress, and inflammation seemed similarly expressed in HFpEF and HFrEF.[59] In this study, transcriptomics revealed 2 apparent, distinct HFpEF subphenotypes—one resembling HFrEF and another with inflammatory and cellular matrix signatures. Such findings suggest that a subgroup of patients with HFpEF may benefit more from already available HFrEF therapies, while other subtypes may benefit from targeted therapies focused on inflammation, proteostasis, and angiogenesis.

Some common pathways have emerged from the transcriptome-wide analyses described above. Most notably, transcripts coding for collagen formation, fibrosis, and immune responses constituted common themes in the literature. However, the heterogeneity of the results in the literature is also compounded by variability in study design, pipelines, and protocols used. Another limitation of many HF transcriptomic studies is the lack of a large enough sample size of myocardial tissue. Blood-derived (whole blood, peripheral blood mononuclear cells, and lymphoblastoid cell lines) RNA has been widely used in transcriptomic studies due to ease of accessibility as well as good surrogacy for some complex diseases, especially ones involving inflammatory components such as HF.[60] Blood-derived RNAs can also have very dynamic expression patterns caused by confounders such as sex, age, and even the time of day blood was drawn. Additionally, associations found in blood, or other tissues/organs not directly implicated in HF pathophysiology, may represent chance or confounded findings. On the contrary, myocardial tissue allows a direct snapshot of the changes occurring in HF and may better improve our understanding of disease development and progression signaling pathways, leading to the development of novel therapeutic approaches. However, myocardial samples are difficult to obtain due to the high risk and limited indication for endomyocardial biopsies. This limitation also applies to other omics such as proteomics and metabolomics. Until a safer and broader use of these biopsies is established, obtaining myocardial transcriptomes at different stages of HF and on a larger scale will remain difficult.

PROTEOMICS

Proteomic analyses include all proteins expressed in a cell or tissue (the proteome) and study their associations with a phenotype in a large-scale, unbiased,

hypothesis-generating scan.[61] Proteins associated with clinical traits can provide insights into the pathogenesis of disease onset or progression, informing therapeutic targets to prevent or treat the disease. Proteomics has bestowed meaningful opportunities to identify proteins associated with the incidence, prognosis, and cardiovascular function of HF.[18,19,62,63] It has also identified protein signatures associated with the pathological differentiation between (1) HF and other diseases, (2) various etiologies of HF, or (3) HF subtypes. These signatures could potentially inform future precision diagnosis and treatment strategies in HF.[64–66] Another strategy to demonstrate the clinical value of protein signatures may be when serial multi-marker testing becomes feasible to generate multi-marker scores.[67] Similar to PRS, these scores can be utilized to predict disease incidence, progression, and outcome. They could also inform drug target discovery as well as treatment response prediction, which can be utilized to further personalize treatment strategies.

To date, most of the protein signatures discovered in HF were identified in the preproteomics era or targeted proteomic studies. Some identified proteins were shared among multiple targeted proteomic studies, which improved the validity of those findings and would be a strength in any other omics findings.[66,68–70] Zhang et al[68] identified and replicated 64 proteins associated with HFrEF hospitalization or cardiovascular death. The significantly associated proteins included a novel protein association, SVEP1 (Sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1), an extracellular matrix protein expressed in vascular smooth muscle that promotes inflammation and atherosclerosis.[68] In their study, SVEP1 displayed an association with HF risk at a magnitude similar to NT-proBNP (N-terminal pro-B-type natriuretic peptide). Regan et al[71] identified and replicated protein signatures associated with HFpEF incidence, hospitalization, and mortality. These proteins were involved in pathways of fibrosis (eg, NEMO and VEGFD), angiogenesis (eg, CLSTN2 and VEGFD), remodeling (eg, CLSTN2 and VEGFD), inflammation (eg, LCN2, KIM1, and Gal-9), renal injury (eg, LCN2 and KIM1), and fatty acid metabolism (eg, AOC3 and SERPINA12).[71]

Proteomics has also made advances toward differentiating HF subtypes more accurately, which could lead to more targeted therapies in the future. Adamo et al[66] found that patients with HFrEF, HF with a mildly reduced ejection fraction, and HFpEF had unique plasma protein signatures, which may reflect distinct biological processes driving disease progression. Complementing this finding, they also found a marked difference in proteomic signatures between ischemic and nonischemic HF, with recovered patients with LV ejection fraction resembling HFpEF more than HFrEF. Some of the proteins included in their signature were later replicated by another group carrying out proteomic comparisons between patients with HFpEF and HFrEF.[65] Reitz et al[70] conducted a global proteomic analysis on LV tissue samples from patients with HF with DCM or ICM. They identified cause-specific proteomic signatures and demonstrated the role of CTNNA3 phosphorylation in regulating cardiac conductance and cell-cell adhesion in the pathophysiology of DCM. These studies help illuminate the distinct pathological pathways between various subtypes or etiologies of HF, which is a crucial first step in identifying personalized drug targets for specific HF subphenotypes.

Although an extensive list of HF-associated proteins has been identified, few proteins have yet to show potential as drug targets. Causal evidence between the proteins and a HF-related trait that could be inferred through approaches such as Mendelian randomization, animal gene knockout, and pharmacological inhibition would greatly strengthen these proteins' potential as drug targets. For example, using a Mendelian randomization approach, researchers from the HERMES and SCALLOP (Systematic and Combined Analysis of Olink Proteins) Consortia incorporated genomic data with proteomic data and identified 8 proteins causally associated with incident HF, with all but one considered potentially druggable.[17] Among their list, inhibitors of galectin-3 and adrenomedullin have already been evaluated in phase 1/2 clinical trials for HF prevention or treatment. A trial of a galectin-3 inhibitor, modified citrus pectin (NCT01960946), did not show significant improvements in collagen markers, echocardiographic measures, or vascular function.[72] Trial results for a monoclonal antibody targeting adrenomedullin, adrecizumab (NCT04252937), have yet to be reported. In addition, LCN2 was found to contribute to cardiac dysfunction by exacerbating ischemia-induced cell death through the suppression of autophagy.[73] *LCN2* also appears to be induced in the cardiomyocytes of mice with mineralocorticoid receptor overactivation as well as mice treated with aldosterone.[74] This induction was prevented by spironolactone treatment. Another potential emerging therapeutic target is AOC3, which was found to increase oxidative stress, cardiac fibrosis, and hypertrophy after MI, an effect that was inhibited through *AOC3* knockdown or pharmacological inhibition with semicarbazide or catalase.[75]

METABOLOMICS

In some cases, small-molecule metabolites may be the ultimate product of the DNA-to-RNA to protein paradigm of cellular information flow.[76] Using spectrometric techniques, the study of the metabolome allows the investigation of known targeted metabolites or the identification of unknown ones using unbiased methods.[76] The prognostic value of circulating metabolites in HF has, in cases such as amino acid panels, outperformed conventional biomarkers such as natriuretic peptides.[77]

However, much remains unknown about the role of the metabolome and its ability to identify potential treatment strategies.

One of the most notable individual metabolites that has emerged from studies in HF is kynurenine, a product generated by tryptophan catabolism. In a metabolomic analysis including 2336 Framingham Study participants, higher levels of kynurenine were associated with decreased LV diastolic dysfunction.[78] A later study found that patients with HFpEF displayed higher levels of kynurenine than patients with HFrEF.[79] Among patients with HFpEF, those with diabetes displayed even higher levels of kynurenine, and those with increased renal function had reduced levels. The study also found that, compared with HFrEF, patients with HFpEF exhibited increased levels of metabolites associated with increased collagen synthesis, inflammation, oxidative stress, impaired lipid metabolism, and downregulated nitric oxide signaling. Thus, microvascular dysfunction may be a target for therapeutic development in HFpEF. Interestingly, kynurenine was also shown to be involved in skeletal muscle function and symptoms of advanced HF, with higher levels associated with inflammation as well as reduced muscle endurance in patients with HFpEF.[80] In a recent study by Bai et al[81], kynurenine-3-monooxygenase inhibition through siRNA knockdown or through treatment with protocatechuic acid reduced isoproterenol-induced oxidative stress, fibrosis, hypertrophy, and cardiac dysfunction.

The application of metabolomics is especially important in HF, as metabolic dysfunction is associated with the disease, particularly in HFpEF. The metabolomic profiles of patients with HFpEF and HFrEF from the Jackson Heart Study were compared, in which increased levels of plasma metabolites such as homoarginine, diacetylspermine, and uridine were identified in patients with HFpEF.[82] Also, metabolites involved in pyrimidine metabolism (orotic acid) and collagen turnover (N-methylproline) differentiated individuals with HFpEF from HFrEF. Hahn et al[83] conducted a metabolomic study of both plasma and endomyocardial biopsies obtained from HFpEF, HFrEF, and non-HF donor controls. Despite the presence of obesity and diabetes, the myocardium of patients with HFpEF showed reduced fatty acid metabolites compared with HFrEF. Ketones as well as metabolites of the tricarboxylic acid cycle and branched-chain amino acids were also lower in HFpEF, showing a lack of use of alternative fuels normally seen in HFrEF. These differences were not seen in plasma, raising an important concern about whether the results from most metabolomic studies conducted in blood would be validated in myocardial tissue and to what extent metabolomics in blood can inform the pathophysiology of HF. Thus, further follow-up of the results from blood/plasma is a crucial step in metabolomics as well as other omics such as proteomics and transcriptomics to better characterize and confirm the role these signals play in the development of HF.

Lipid biology is undoubtedly important in the development of atherosclerotic disease, but lipidomics may also be important in HF for understanding the nuances of the biological functions of lipid molecules and identifying metabolites with lipotoxic effects. Although lipidomics is often grouped within metabolomics, it could be categorized as a stand-alone omic method. Two prospective studies (discovery and validation cohorts) in patients showed that baseline plasma concentrations of ceramide C16:0 and diacyl phosphatidylcholine C16:0/C16:0 were associated with increased HF risk.[84] Lipidomic patterns were also identified through the discovery of HF-associated lipidomic network clusters utilizing machine learning, followed by the identification of HF-associated single metabolites within these clusters through regression-based methods.[84] Reducing the accumulation of serum ceramides was associated with improvement of cardiac dysfunction in a doxorubicin-induced HF mouse model.[85] Thus, targeting ceramides may be a promising treatment option, and further studies in other preclinical models of HF are warranted. After identifying apoC-III, apoC-II, and apoE as the apolipoproteins most strongly associated with a major adverse cardiovascular event (ischemic stroke, MI, or cardiovascular death), Pechlaner et al[86] found that inhibition of hepatic apoC-III synthesis with the antisense oligonucleotide volanesorsen also reduced plasma apoC-III as well as triglycerides, low-density lipoproteins, apoC-II, and apoE in 2 different patient cohorts. This demonstrates that utilizing therapeutic targets from omics data may not only represent a novel strategy but could potentially reduce disease risk through a variety of favorable effects.

The study of the microbiome has also been emerging in the search for novel therapeutic targets for HF. Recent advances have linked the human gut microbiota with the development of cardiovascular diseases with multiple studies revealing its contribution to HF.[87] One study followed up on 106 patients with HF due to DCM and found a metabolomic signature predictive of mortality.[88] The top individual metabolite, trimethylamine-N-oxide (TMAO), was significantly elevated in deceased patients with DCM. TMAO is generated by gut microbiota from dietary precursors rich in choline, phosphatidylcholine, and L-carnitine. In fact, higher blood levels of TMAO have previously been linked to increased mortality risk in patients with HF.[89,90] Although the evidence about a link between gut metabolites, specifically TMAO and HF, has compiled, the mechanistic pathway remains unclear.

The complementary findings or occasional overlap between metabolomics and emerging fields such as lipidomics and microbiomics emphasize the need to study the interrelationships between different omics data and the advantages of multiomics profiling in strengthening the identification of novel therapeutic targets for HF.

MULTIOMICS

Given the complex mechanisms across multiple tissues and organs in HF, the use of multiomic techniques provides an opportunity to connect multiple biological processes to better understand underlying pathophysiological mechanisms.[91] A sequential strategy assesses omic data types individually, analyzing each layer in the context of the previously analyzed layer, which can permit the inclusion of established biological relationships between omics types. Integrative strategies analyze all available omic data together simultaneously, taking into account the interactions between omic layers and their complementary roles; however, the methods for integrative analyses continue to be developed and are more complex.[91] To date, the lack of large HF patient populations with multiple types of omics data available has likely hampered the number of HF multiomic analyses published. However, the few that have been published demonstrate the potential future insights that can be gained by these approaches.

Repository and available data sets have been utilized to integrate different omics data in the study of HF mechanisms. In a study comparing DCM and ICM to controls, publicly available data sets of transcriptomic and proteomic data were sequentially layered. Differentially expressed genes and proteins that were common between DCM and ICM included those involved in cardiac remodeling (*CA3*, *UCHL1*, *AEBP1*, and *THBS4*) and cardioprotection (*SOD3* and *HSPA2*). Genes and proteins involved in muscle tissue development pathways were differentially expressed in only DCM (*MYH6* and *SERPINA3*), whereas cardiac remodeling and immune cell activation and migration were differentially expressed only in ICM (*COL14A1* and *LUM*).[92] These results seem similar to those reported by Kanapeckaitė et al,[93] who also integrated transcriptomic and proteomic data from patients with DCM and ICM. One of the identified potential therapeutic targets was ubiquitin C-terminal hydrolase L1 (*UCHL1*), a deubiquitinase that regulates protein homeostasis and appears upregulated in cardiomyocytes post-MI.[94] Additionally, *UCHL1* has been implicated in cardiac hypertrophy in both mouse and human heart samples. Administration of the UCHL1 inhibitor LDN-57444 reduced hypertrophy in the murine model, indicating *UCHL1* as a potential HF drug target for future studies.[95]

In another sequential multiomics analysis, an initial proteomic analysis of Black participants with LV hypertrophy from the Jackson Heart Study identified 13 proteins in plasma that were associated with LV mass, with the strongest association observed with leukotriene A4 hydrolase (LTA_4H). This association was validated with metabolomic data indicating associations between several LTA_4H downstream metabolites and LV mass.[96] LTA_4H is an epoxide hydrolase involved in the synthesis of the proinflammatory mediator leukotriene B4, which has been associated with an increased risk of MI in the general population.[97] LTA_4H also appears to possess aminopeptidase activity that can degrade some neutrophil chemoattractants.[98] Thus, LTA_4H activity can have opposing activating and deactivating effects on inflammation. Previously developed LTA_4H inhibitors, such as veliflapon (DG-031), have not shown clinical benefits in patients with MI; however, recent efforts to develop more specific compounds that only inhibit the proinflammatory effects have been conducted, indicating this target may still have potential in cardiovascular diseases.[98] Therefore, these studies demonstrate that sequential multiomic approaches—analyzing top GWAS findings in subsequent omic layers—are feasible and can identify novel potential drug targets.

Multiomic analyses have also been completed in human myocardial tissue. A study of biopsy tissue from 41 patients with DCM and from 31 controls compared epigenomic, transcriptomic, and genomic data sequentially to identify biomarkers and epigenetic susceptible genomic regions. Three CpG loci were significantly differentially expressed, and concordant differential gene expression of *PLXNA2* and *RGS3* was associated with 2 of the CpG loci.[99] *RGS3*, regulator of G protein signaling 3, is a member of a family of GTPase activating proteins that can deactivate the alpha subunits of G proteins and has been implicated in the regulation of cardiac function.[100,101] The expression of *RGS3* and RGS3 protein abundance is higher in end-stage failing hearts, and the potential role of RGS proteins is being studied as drug targets in diseases such as cancer.[102,103]

Levin et al conducted a large multi-ancestral and multi-cohort GWAS meta-analysis on 115 150 cases of all-cause HF and 1 550 331 controls, identifying and replicating 47 risk loci. The utilization of multi-trait colocalization and integration of transcriptome-wide association data from the Genotype-Tissue Expression project prioritized genes for further study. Highly prioritized genes included *BCKDHA*, *PROM1*, *CLCNKA*, *PRKCA*, and *BAG3*.[104] Two examples, *PRKCA* and *BAG3*, seem to demonstrate the most promise. *PRKCA*, protein kinase C alpha, is a calcium- and lipid-activated serine/threonine kinase that regulates contractility and calcium handling in the heart and is stimulated in HF.[105] The knockout of *Prkca* in multiple mouse models of HF was associated with improved long-term survival.[105] Furthermore, in a swine model of HF, the administration of ruboxistaurin, a protein kinase C alpha and beta inhibitor, increased contractility and reduced end-diastolic volumes, which further supports the potential of *PRKCA* as a druggable target.[106] *BAG3* encodes the Bcl-2–associated athanogene cochaperone 3 protein, which has been implicated in the structural integrity of cardiac muscle.[107] Rare variants in *BAG3* were discovered initially in a GWAS of familial DCM cases, and continued research has implicated

their role in HF development.[108] The administration of an adeno-associated virus expressing BAG3 in a HF mouse model significantly improved the left ejection fraction.[109] This early study implicates *BAG3* as a potential target for gene therapy; however, hurdles related to potential pro-oncogenic off target effects would require further study.[110]

In another integrative study of over 8000 participants from the Framingham Heart Study, Andersson et al integrated genomic, methylomic, and transcriptomic data from blood to identify genes associated with HF diagnosis as well as echocardiographic measures of LV dysfunction and remodeling. The genes most strongly associated with increased risk of HFrEF development were *TSPAN16*, *RAB11FIP3*, *RAC1*, *RPA2*, and *F13B*.[111] Rac family small GTPase 1 (*RAC1*) activates NADPH oxidases (*NOX1* and *NOX2*), which produce reactive oxygen species that have previously been implicated in HFpEF development.[112,113] *RAC1* appears to be a critical mediator in the development of cardiac hypertrophy in mice.[114] Atorvastatin decreased Rac1 protein expression and improved cardiac function in an animal model.[115] However, clinical trials of statins have not yet confirmed these findings, and debate remains on the clinical utility of statin therapy in HF.[116,117] Additionally, a *RAC1* inhibitor, NSC23766, has shown a reduction in cardiac remodeling and cellular hypertrophy in animal and cellular studies, demonstrating *RAC1* as a potential druggable target.[118,119] Moreover, Andersson et al[111] identified the top 5 genes associated with prevalent HFpEF as *HPCAL1*, *PTTG1IP*, *ZNF843*, *SGLT2*, and *SNX25*. While the results of this study did not inform the EMPEROR-Preserved trial of SGLT2 inhibitors in HFpEF, given the trial's results and the subsequent Food and Drug Administration approval of SGLT2 inhibitors for HFpEF in 2022,[35] this study still highlights the potential for integrative multiomic methods to identify druggable targets.

Multiomic techniques allow for corroboration of findings between distinct data types, which improves the validity of omic study results, and can help identify the strongest candidates among the noise of many apparently significant associations. For example, in a study of hypertrophic cardiomyopathy, which utilized RNAseq, ChIPseq, and proteomics, while thousands of regions, genes, and proteins were implicated in individual omic layers, there were only 53 genes with consistent direction across the omic layers.[120] In addition, these methods can provide additional insight into how these findings integrate into the biological pathways that drive HF progression. Single-platform omics data have led to several findings to date, but with the complex etiologies and systemic effects of cardiovascular diseases, the interactions between different omics data would likely be better elucidated by integrated multiomics analyses.[121,122] For example, correlating RNAseq data to metabolomics data can identify gene clusters involved in immune regulation that are associated with individual lipid changes in CAD, providing insight on the interaction of distinct underlying biological processes in relation to a disease state.[121,122] Individually, single omics studies could have found the association of each of these processes with the disease but likely would not have linked both together.[121,122] In a similar complex disease state such as HF, integrated multiomics have the potential to provide novel insight by finding interactions between different biological processes linked to HF pathophysiology. While to date, the use of multiomic techniques has not directly led to a published druggable target in HF, the identification of targets for which early preclinical work is proving promising and for which drugs have been developed and approved demonstrates its potential. As omic data becomes increasingly available for patients with HF, the role of multiomic analysis for drug target identification and in the drug development pipeline will likewise increase.

CURRENT PROGRESS AND FUTURE DIRECTIONS

While omics research has provided several candidates for future studies that are potentially associated with HF development and progression (Table), these data have yet to provide the basis for new therapeutics. This is partly due to the limited data in some omics areas, such as epigenomics and metabolomics. In addition, barriers exist that prevent the widespread utility of omics findings. One is the failure of many omics findings to be replicated by independent research groups or validated using other experimental techniques. Some of these failures may be due to data artifacts stemming from difficult-to-address issues such as small numbers of patients who possess a given genetic variant or who express a specific protein or metabolite. Others are likely due to the differing methods of data processing and analysis that are used. Such methodological inconsistencies, when coupled with phenotypic differences often present between study populations, make it difficult to arrive at consistent results, even between 2 studies that, on the surface, seem similar. More formalized procedures for data processing and analysis across omic data types would greatly address this barrier. In addition, many of the studies described above reported genes, proteins, or metabolites linked to various biological pathways or biological functions that were associated with a particular phenotype of interest. However, the genes involved in each pathway may differ depending on the data source. Furthermore, the evidence base required to connect a gene to a pathway is not always clearly delineated and is often inconsistent among sources. This makes these types of results more difficult to interpret and can lead to assumptions of pathway involvement that are not always well supported.

Table. Summary of Potential Therapeutic Targets for HF Stemming From Multiple Omics Studies

Gene (protein or metabolite)	Omic methods in which identified	Phenotype(s)
ACTN2	Multiomics (Multiple Studies)	HF,[104] HCM[123]
AEBP1	Multiomics (Multiple Studies)	DCM,[92,93] ICM[92]
ALPK3	Multiomics, Genomics	HF,[104] HCM,[124] myocardial mass,[16] LV measures[12]
APOA1	Multiomics (Multiple Studies)	ICM[92,93]
ARHGAP1	Multiomics, Genomics	DCM,[93] ICM,[93] HCM[120,125]
ATP2A2	Multiomics (Multiple Studies)	ICM,[93] HCM[120]
BAG3	Multiomics, Genomics	HF,[4,104,126] DCM,[127] idiopathic DCM,[128] HCM,[124,127] LVEDV,[12,127,129] LVESV,[12] LVEF[12]
BCAT2 (branched-chain amino acids)	Multiomics, Metabolomics	ICM,[93] HFpEF[83]
BGN	Multiomics (Multiple Studies)	ICM,[92] HCM[120]
CA3	Multiomics (Multiple Studies)	DCM,[92] ICM,[92] HCM[120]
CDH2 (CADH2)	Genomics, Proteomics	Resting HR,[14] HFpEF[71]
CDKN1A	Multiomics, Genomics	HF,[4,104,126] DCM,[127] HCM[124,127]
CLCNKA	Multiomics, Genomics	HF,[104] LVEDV,[127] LVEF,[12] LV mass to volume ratio[12]
COL14A1	Multiomics (Multiple Studies)	DCM,[93] ICM[92,93]
COX17	Multiomics, Epigenomics	ICM,[93] HF[31]
CSTB (CYTB)	Multiomics, Proteomics	HF,[130] HFpEF[71]
DNAJC18	Multiomics, Genomics	HF,[104] HCM[127]
EFEMP1 (FBLN3)	Multiomics, Proteomics	ICM,[93] HFrEF[65]
FGF12	Multiomics, Genomics	HCM,[120] idiopathic DCM[131]
FTO	Multiomics, Genomics	HF[4,104,126]
GPD1L	Multiomics (Multiple Studies)	ICM,[93] HCM[120]
GTF2I	Multiomics, Genomics	HF[104,126]
HBA2	Multiomics, Proteomics	DCM,[92] ICM,[92] HF in Afib[69]
HBB	Multiomics (Multiple Studies)	DCM,[92] ICM[92,93]
HSPA2	Multiomics (Multiple Studies)	DCM,[92] ICM,[92] HCM[120]
KLHL3	Multiomics, Genomics	HF[4,104,126]
LPA	Multiomics, Genomics	HF[4,104,126]
LTBP2	Multiomics (Multiple Studies)	ICM,[92] HCM[120]
LUM	Multiomics (Multiple Studies)	ICM,[92,93] HCM[120]
MAP4	Multiomics (Multiple Studies)	ICM,[93] HCM[120]
MAPT	Multiomics, Genomics	HF,[104] myocardial mass[16]
MFAP4	Multiomics (Multiple Studies)	DCM,[93] ICM[92]
MMP11	Multiomics, Genomics	HF,[104] HCM,[124] LV measures[12]
MTSS1	Multiomics, Genomics	HF,[104] DCM,[127] LVESV,[12] LVEF[12]
MYH6	Multiomics, Genomics	DCM,[92,93] HCM,[120] HR,[15] resting HR[14]
MYH7	Multiomics, Genomics	ICM,[93] resting HR[14]
MYO1C	Multiomics, Genomics, Epigenomics	HF,[104] LVEDV,[129] DCM[99]
NDRG2	Genomics, Epigenomics	DCM,[99] resting HR[14]
NEDD4L	Multiomics (Multiple Studies)	Incident HFpEF,[111] HF[104]
NEO1	Multiomics, Genomics	Prevalent HFpEF,[111] resting HR[14]
NMB	Multiomics, Genomics	HF,[104] DCM,[127] LV measures,[12] myocardial mass[16]
NPC1	Multiomics, Genomics	HF[104]
NPPA	Multiomics, Genomics, Transcriptomics	DCM,[93] ICM,[93] HCM,[120] end-stage HF,[56] NT-proBNP[6]
NPPB (NT-proBNP)	Genomics, Proteomics	Incident HF,[62,63] LV mass,[63] LV diastolic dimension,[63] left atrium diameter,[63] incident HFpEF,[65] incident HFrEF,[65] prevalent HFrEF,[68] NT-proBNP[6]
PDK4 (TCA cycle metabolites)	Multiomics, Metabolomics	HCM,[120] HFpEF[83]

(*Continued*)

Table. Continued

Gene (protein or metabolite)	Omic methods in which identified	Phenotype(s)
PHIP	Multiomics, Genomics	HF[104,126]
PITX2	Multiomics, Genomics	HF[4,104,125,126]
POM121C	Multiomics, Genomics	HF[104,126]
PRELP	Multiomics, Proteomics	HF,[130] HFpEF[71]
PRKCA	Multiomics, Genomics	HF,[104] DCM,[127] HCM[124,127]
RPL22	Multiomics, Genomics	Incident HFpEF,[111] HF[104]
RXRG (acylcarnitines)	Genomics, Metabolomics	HR in HFrEF,[83] HFrEF[132]
SMG6	Multiomics, Genomics	HF,[104,126] aortic root size[13]
SNCA (SYUA)	Multiomics, Proteomics	HCM,[120] HF in Afib[69]
SOD3 (SODE)	Multiomics, Proteomics	DCM,[92] ICM,[92] LV diastolic dimension[63]
SPATS2L	Multiomics, Genomics	HF[104,126]
STRN	Multiomics, Genomics	HF,[104] HCM[120]
SURF1	Multiomics, Genomics	HF[4,104]
SYNPO2L	Multiomics, Genomics	HF,[104,126] HCM,[120,127] LVEDM,[129] myocardial mass[16]
THBS4	Multiomics, Transcriptomics	DCM,[92] ICM,[92] HCM,[120,133] hypertrophy[120,133]
TTN	Multiomics, Genomics	DCM,[93,127] HF,[104] HCM,[124] LVEDV,[12,129] LVEDM,[129] LVESV,[12] LVEF,[12] LV mass,[12] resting HR[14]
UCHL1	Multiomics (Multiple Studies)	DCM,[92] ICM,[92] HCM[120]
ZNF592	Multiomics, Genomics	HF,[104] HCM,[127] LV mass to volume ratio[12]

Afib indicates atrial fibrillation; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ICM, ischemic cardiomyopathy; LV, left ventricular; LVEDM, left ventricular end-diastolic mass; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and TCA, tricarboxylic acid.

Despite these barriers, omics are still expected to continue providing novel insights into HF—a disease in need of additional therapeutic options. Omics studies also have the potential to monitor treatment effectiveness at the molecular level, such as in the case of a MI mouse model where proteomics was used to evaluate if cardiopoietic stem cell therapy reversed the protein level changes induced by MI.[134] Ongoing developments in omics techniques could potentially advance the field further. For example, data-independent acquisition proteomics—an innovative mass spectrometry method where every analyte present in a sample is included regardless of whether the identity is known—offers broader coverage with improved accuracy and reproducibility.[135] In addition, multiomics assaying techniques such as CITE-seq,[136] REAP-seq,[137] or scTrio-seq[138,139] are capable of measuring multiple omics from the same set of samples. Such advances in measurement or experimental techniques, combined with more elaborate computational methods such as matrix-factorization-based methods or neural network-based methods, could significantly improve the ability to combine omics data types and identify complex patterns between them.[140] Multiomics provides the most promise to provide novel insights on HF treatment targets, as combining omics data provides the ability to validate findings on a much larger scale than current methods such as in vitro functional experiments. Moreover, by providing insight into how different omics interact with each other in vivo, multiomics has the ability to determine whether the differences observed in a particular transcript, protein, or metabolite drive HF disease progression or are themselves driven by HF progression. These types of mechanistic insights often require multiple parallel data sources.

Multiomics analyses possess additional challenges beyond those encountered in single omics analyses. First, methods for combining and analyzing multiple, often disparate, large data types are still being developed. Second, as patient sample sizes grow, the total amount of data for analysis becomes so large that current methods for single omics data can become impractical for multiomics data. Thus, multiomics appears to provide an excellent opportunity for artificial intelligence (AI) to address these issues and meaningfully move the field forward. However, using AI to aid multiomic analyses would not be without its own barriers to overcome. First, such AI methods have yet to be developed. While some investigators have begun using AI to analyze multiomic data from animal models,[141] much work is still needed to develop reliable and reproducible methods to analyze this type of data. This includes information related to AI analysis performance compared with conventional analytical methods and the availability of early examples of AI-derived omics signals that are later functionally validated. A successful use of AI was shown by Cheng et al[142] when the group developed a model capable of predicting the pathogenicity of

missense variants using sequence data. A large majority of missense variants have still not been annotated, so having such a tool can help with the functional prediction of variants or potentially other changes, such as protein structure, which would complement omics findings and advance the development of specific treatments. Reproducibility of results will be particularly important with AI because a noted limitation of many AI-based analyses is that the specific models used can change each time the analysis is run. Such an issue is further compounded by the barriers noted above related to the complexity of data processing, analysis, and interpretation of omics data.

A particularly promising use of AI could be in improving the precision of therapeutic strategies in HF. We now have extensive evidence that HF is a heterogeneous disease, likely meaning that heterogeneous treatment strategies will be required. These subphenotypes are likely to have significant overlap related to patient presentation and the underlying dysregulated biological pathways that are involved. It would also be reasonable to assume that not every patient will fit into a subphenotype. AI could be a valuable resource to assist with identifying patients likely to benefit from a specific treatment regimen given their presentation. Such a strategy should improve therapeutic efficacy for patients with HF and provide a successful example of precision medicine to follow for other cardiovascular diseases.

CONCLUSIONS

In a complex and multifactorial disease such as HF, omics data can provide novel insight into the mechanisms underlying HF development or progression. Significant and functionally validated findings may enable more specific categorization of HF subphenotypes, potentially allowing for the repurposing of already available drugs to target the specific pathophysiology. Such findings could also lead to the discovery of novel therapeutic targets, allowing the development of new and tailored treatment modalities. While several genomics and transcriptomic analyses have been published in patients with HF, there are fewer global proteomics, epigenomics, metabolomics, and very few published multiomics studies. Thus, the greatest impact of omics research in HF is likely yet to come. Additional omics research is needed, particularly in multiomics. AI would likely be a useful resource for both analyzing the large amount of data produced by these research methods and optimizing therapeutic strategies for patients. A major challenge that is especially important for a heterogeneous syndrome such as HF is the paucity of reproducible omics data, making it more difficult for researchers to have meaningful interpretations for their findings. With more robust, comprehensive, and reproducible HF omics data sets, significant advances can be made to identify, validate, and use novel targets for the development of new therapies for HF.

ARTICLE INFORMATION

Affiliation

Center for Pharmacogenomics and Precision Medicine, Department of Pharmacotherapy and Translational Research, University of Florida College of Pharmacy, Gainesville, FL.

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