REVIEW

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Epigenetic remodeling in heart failure with preserved ejection fraction

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Purpose of review
In this review, we critically address the role of epigenetic processing and its therapeutic modulation in heart failure with preserved ejection fraction (HFpEF).

Recent findings
HFpEF associates with a poor prognosis and the identification of novel molecular targets and therapeutic approaches are in high demand. Emerging evidence indicates a key involvement of epigenetic signals in the regulation of transcriptional programs underpinning features of HFpEF. The growing understanding of chromatin dynamics has led to the development of selective epigenetic drugs able to reset transcriptional changes thus delaying or preventing the progression toward HFpEF. Epigenetic information in the setting of HFpEF can be employed to: (i) dissect novel epigenetic networks and chromatin marks contributing to HFpEF; (ii) unveil circulating and cell-specific epigenetic biomarkers; (iii) build predictive models by using computational epigenetics and deep machine learning; (iv) develop new chromatin modifying drugs for personalized management of HFpEF.

Summary
Acquired epigenetic signatures during the lifetime can contribute to derail molecular pathways involved in HFpEF. A scrutiny investigation of the individual epigenetic landscape will offer opportunities to develop personalized epigenetic biomarkers and therapies to fight HFpEF in the decades to come.

Keywords
biomarkers, epigenetics, heart failure with preserved ejection fraction, personalized medicine

INTRODUCTION

Contrary to genetic information, epigenetic signals mirror the contribution of environmental stress and lifestyle changes, and their reversible nature offers a promising opportunity to monitor disease states. Recent studies have unveiled epigenetic networks implicated in the regulation of cardiac hypertrophy, fibrosis, and microvascular dysfunction, key features of heart failure with preserved ejection fraction (HFpEF). The prevalence of heart failure (HF) keeps rising each year, and HFpEF is responsible for more than half of the new diagnoses [1,2]. Such increase in HFpEF prevalence can be mainly attributed to the exponential increase in cardiometabolic disturbances, such as obesity, and type 2 diabetes [3,4]. Indeed, obesity and prediabetes are among the most powerful predictors of incident HFpEF over the next decades, both in men and women, although the association is stronger in the latter group [2,5]. HFpEF is a complex syndrome characterized bysigns or symptoms of congestion, preserved or mildly abnormal left ventricular (LV) systolic function (EF $>$ 50%, left ventricular end-diastolic volume index $<$97 mL/m^2), and diastolic dysfunction [6,7]. It is characterized by structural and cellular alterations, including cardiomyocyte hypertrophy, fibrosis, and inflammation, all leading to an inability of the left ventricle to relax properly. HFpEF often clusters with other comorbidities which successfully contribute to worsening the patient's outcome, with

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KEY POINTS

- Emerging evidence indicates a key involvement of epigenetic signals in the regulation of transcriptional programs underpinning features of HFpEF.
- Most epigenetic modifications are rather stable over life, suggesting they might be employed to predict cardiovascular alterations years before the development of any symptom by combining computational biology with machine learning approaches.
- A deeper understanding of the individual epigenetic landscape will offer opportunities to develop personalized epigenetic therapies to fight HFpEF in the decades to come.

an annual mortality of approximately 22% [8,9▪]. Comorbidities such as hypertension and obesity promote a chronic state of inflammation, oxidative stress, endothelial dysfunction, and cardiomyocyte stiffness which further aggravates cardiac dysfunction [4]. Medical advances have developed efficient and specific treatments of HF with reduced ejection fraction (HFrEF) by acting on the neuro-humoral axis, however, breakthrough therapies for the treatment of HFpEF remain to be identified. As a result, the prevalence of HFrEF has declined over the last few decades, whereas the prevalence of HFpEF is skyrocketing, and accounts for more than 50% of all HF cases [10].

EPIGENETIC SIGNALS AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

Although inborn genetic variation is strongly involved in the pathogenesis of several cardiomyopathies, most HF cases - including HFpEF - are the result of gene-environment interactions involving epigenetic control of gene transcription. Emerging evidence indicates that the epigenetic variation constitutes a fundamental biological layer that amplifies inter-individual diversity as well as disease heterogeneity and complexity [11]. The epigenome - which includes changes of DNA methylation, histone posttranslational modifications (PTMs), and noncoding RNAs (ncRNAs) - can faithfully reflect life experiences and environmental stress (e.g. metabolic, toxic, or psychological stress) throughout life [12]. Of note, acquired epigenetic signals can be transmitted to the offspring. This form of heredity involves the transmission of the effects of parental exposure to the offspring through epigenetic changes in the germline [13]. The concept of 'epigenetic inheritance' set the basis for a new field of investigation where transmissible epigenetic signals can account for early disease phe-notypes. Inherited epigenetic signals lead to premature transcriptional alterations and early cardiovascular disease (CVD) phenotypes (endothelial dysfunction, diastolic dysfunction, LV hypertrophy, and skeletal muscle abnormalities) which may start to manifest already during adolescence. In this context, epigenetic inheritance may contribute to the current pandemic of cardiometabolic disturbances, inflammatory changes, and comor-bidities, all casually implicated in HFpEF development [11,14].

EMPLYOING EPIGENETICS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION PHENOMAPPING

Besides their causal role, epigenetic changes can be leveraged as potential biomarkers in the setting of CVD and HF. Most epigenetic modifications are rather stable over life, suggesting they might be employed to predict cardiovascular alterations overtime [15,16▪,17]. Three keystones support the use of epigenetic modifications as putative biomarkers: (i) the epigenetic landscape often reflects environmental exposure and lifestyle changes, (ii) epigenetic signals can be measured in tissues and fluids (e.g. saliva, plasma, urine), and once acquired are relatively stable over time, and (iii) they can be detected during early stages of diseases [18].

Recent evidence suggests that epigenetic information can be used to elaborate predictive models by combining computational biology with machine learning approaches [19,20]. The latter approach has been validated in cohorts of patients with cancer, neurodegenerative and autoimmune disease and the results are encouraging [18,20]. As an example, a recent study employing machine learning-based methods was able to identify 18 specific methylation regions involved in autoimmune diseases and food allergies [20]. In a few years, the implementation of computational epigenetics might be able to: (i) interpret large epigenomic datasets and extrapolate relevant information for the development of personalized approaches, (ii) test existing epidrugs and develop new ones based on computational and predictive methodologies, (iii) create individualized epigenetic landscapes for each patient and extrapolate the implication for their health [16▪].

The potential application of epigenetic biomarkers in the clinic is outlined by several studies. Whole-genome methyl-binding domain-capture sequencing was shown to discriminate between patients with or without HF based on 48 specific differentially methylated regions [21]. Another study identified several epigenetic loci associated

with HF that were replicated in independent studies and were involved in modulating central signaling pathways in the heart [22]. Moreover, these loci were consistent across tissues, making them good candidates for novel biomarkers. Similarly, other studies have shown that subtypes of HF associate with specific patterns of DNA methylation [23]. Somatic mutations of DNMT3A and TET, responsible for addition and removal of DNA methylation respectively, were recently associated with the appearance of leucocyte clones (clonal hematopoiesis of indeterminate potential, CHIP), a known risk factor for the development of CVD such as myocardial infarction and stroke [24]. Of note, CHIP increases with age and is present in 10% of people aged >70 years. Mutations in either DNMT3A or TET2 were found in 18.5% of patients with HF and were independently associated with HF re-hos-pitalization and death [25]. A recent analysis conducted on 5000 women from the Women's Health Initiative revealed that CHIP-related mutations are associated with the development of HFpEF [26]. In line with these results, mouse models of CHIP display myocardial inflammation and diastolic dysfunction [27]. Taken together, these data suggest that aging derails pathways controlling DNA meth-ylation, with subsequent transcriptional alterations fostering pathological cardiac remodeling.

GENDER-RELATED EPIGENETIC BIOMARKERS

HFpEF is more prevalent in women as compared to males (60%) and usually affects postmenopausal women with at least one comorbidity such as hypertension or diabetes [2]. Women usually develop less ventricular dilation but more cardiac stiffness, possibly due to different susceptibility to fibrotic accumulation and differences in calcium handling [28]. Indeed, women affected by HFpEF have higher levels of propeptide for type I collagen [29]. Hormones also play a central role in these differences. For example, estrogen and androgen receptors can recruit histone acetyltransferases CREB binding protein (CBP) and E1A binding protein p300 (EP300) thus modulating the expression of genes implicated in cardiac fibrosis [30].

EPIGENETIC PROCESSING IN CARDIOMETABOLIC HEART FAILURE WITH PRESERVED EJECTION FRACTION

The unhealthy lifestyle and environmental exposure can, over time, lead to detrimental changes in the epigenetic landscape thus promoting a condition known as 'metabolic inflammation'. Such a combination of dysmetabolic and pro-inflammatory signals was recently identified as a crucial driver of HFpEF [4,31] (Fig. 1). Chromatin remodeling, not only in the heart but also in other tissues, can contribute to the development of metabolic inflammation and HFpEF. Specifically, visceral and epicardial adipose tissue secretome may foster stiffness and diastolic dysfunction in a paracrine manner [32,33]. Epigenetic studies in adipose tissue have identified specific epigenetic changes in the detrimental transition from brown to white adipose tissue, thereby enhancing the secretion of pro-inflammatory cytokines such as IL-6 [34]. Furthermore, genome-wide epigenetic studies in obese patients revealed important changes in DNA meth-ylation in genes involved in fibrosis and metabolism such as COL9A1 and GATA4 [35].

CHROMATIN MARKS

High-throughput pyrosequencing showed that the distribution pattern of H3k4me3 and H3k9me3 were significantly different in patients with or without HF and that most changes occurred on genes involved in calcium handling and cardiac contractility [36]. A similar study identified more than 9000 candidate enhancers involved in hypertrophy whose activity was different in HF. Specifically, a reduction in H3k9me3 and H3k27me3 was associated with the upregulation of genes involved in the development of cardiac hypertrophy [37]. Similarly, it was shown that H3k27ac and H3k36me3 were predictive markers of HF. Taken together, this evidence suggests that specific changes in DNA methylation and histone PTMs could be invaluable to build epigenetic maps of HF risk [16▪,38]. The main problem when it comes to histone PTMs is that they can only be assessed in tissues or isolated cells. However, the recent discovery and validation of circulating cell-free nucleosomes in human plasma could represent a promising approach to study cell-specific chromatin marks as biomarkers of HFpEF [39].

NON-CODING RNAs

NcRNAs have been extensively studied as potential biomarkers of CVD and HF. A combination of 5 microRNAs (miR-30c, -146a, -221, -328, and -375) was shown to differentiate between patients HFpEF and HFrEF [40]. Of interest, these 5 miRNAs are functionally involved in extracellular matrix (ECM) remodeling, inflammation, and fibrosis strengthening their potential involvement in HFpEF. MiR-3135b and miR-3908 were also reported as reliable markers in HFpEF patients [41]. Another

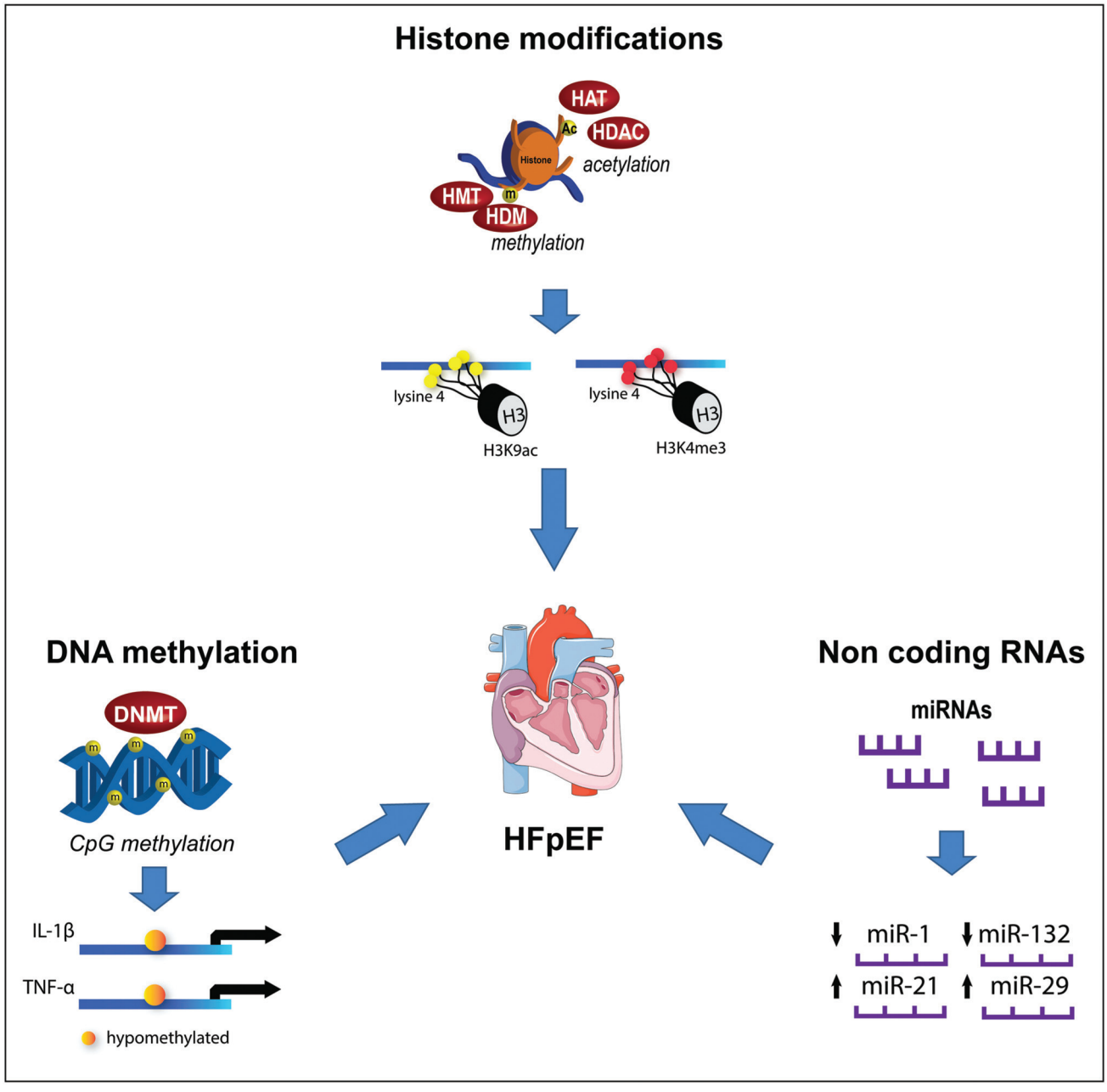

FIGURE 1. Epigenetic changes potentially involved in HFpEF. Alterations of DNA methylation, histone modifications and ncRNA landscape promote transcriptional changes leading to key HFpEF features namely cardiac fibrosis, hypertrophy and microvascular dysfunction. The main epigenetic signals are shown. HFpEF, heart failure with preserved ejection fraction; ncRNAs, noncoding RNAs.

study showed that miR-190 was independently associated with a diagnosis of HFpEF, and was able to discriminate HFpEF from HFrEF [42].

EPIDRUGS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

Over the last decade, a growing number of epigenetic compounds were unveiled and tested for the treatment of a wide spectrum of human diseases [43]. Of note, several of these drugs have already been approved by the Food and Drugs Administration (FDA) (Table 1) [44–51]. Inhibitors of histone deacetylases (HDAC) - such as sodium butyrate – have shown to blunt myocardial inflammation (i.e. NF-kB signaling) and oxidative stress in experimental models of HF [52,53]. The FDA-approved Vorinostat (SAHA), a potent pan-inhibitor of classes I, II, and IV HDACs, has been shown to modulate the autophagic response in the heart thus preventing

Table 1. Epidrugs in HFpEF

Drug	Epigenetic editing	Mechanism of action	Potential application in HFpEF
JQ1 [56]	BET inhibitor	Inhibition of NF-κB and TGF-β signaling with subsequent prevention pressure overload-induced hypertrophy and fibrosis	Effects on inflammation, fibrosis, LV remodeling and diastolic dysfunction
Apabetalone (RVX-208) [56–59,60▪]	BET inhibitor	Prevents endothelial inflammation and suppress expression of pro-inflammatory cytokines such as IL-6 and TNF-α).	Effects on microvascular dysfunction and metabolic inflammation
Remlarsen [16▪]	miR-29 mimic	miR-29 is a powerful modulator of fibrosis and ECM remodeling	Antifibrotic effect, improvement of LV relaxation and exercise tolerance
CDR132L [62,63]	Synthetic lead-optimized oligonucleotide inhibitor of miR-132	Improvement of diastolic dysfunction and left atrial remodeling	Promising candidate in HFpEF for its beneficial effects on LV relaxation and cardiac hemodynamics
Vidaza (5-azacytidine) [44]	DNA methylation inhibitor	Inhibits DNMT with subsequent demethylation of genes implicated in vascular homeostasis (i.e. eNOS)	Induces endothelial gene expression and endothelial differentiation through DNA hypomethylation.
Tranylcypromine [44–47]	Irreversible LSD1 inhibitor	Improves angiogenesis through the inhibition of LSD1	Enhances the function of endothelial progenitors in vascular repair
Trichostatin A (TSA) [48,49]	Class I HDAC inhibitor	Suppresses NF-kB target genes and TNFα transcription in the heart. Prevents connexin40-driven remodeling	Acts as an antifibrotic and antihypertrophic drug; prevents pathological LV remodeling and dysfunction
Vorinostat (SAHA, Zolinza) [54]	Class I, II, and IV HDAC inhibitor	Modulates inflammatory response, autophagic flux and fibrosis. Prevents myocardial ischemic injury.	Improves the sarcoendoplasmic reticulum Ca^{2+}-ATPase activity in cardiac myocytes; reduces inflammatory processes; improves metabolic efficiency while blunting myocardial hypertrophy in experimental models of HF
Hydralazine [50,51]	Indirect effect on DNA methyltransferase activity	Increases sarcoplasmic reticulum Ca^{2+}-ATPase and modulates calcium homeostasis in cardiomyocytes	SERCA2a upregulation; increase in Ca^{2} transients and sarcoendoplasmic reticulum calcium content with subsequent improvement of cell contractility
SGLT2 inhibitors (empagliflozin and dapagliflozin) [69–71]	Indirect effect on DNA methylation, histone PTMs and ncRNAs (e.g. miR30e–5p and miR199a-3p)	Act on chromatin modifiers by increasing ketone 3-hydroxybutyric acid; modulate the expression of ncRNAs	Improve hemodynamics in HF by increasing renal protection and reducing cardiac fibrosis

DNMT, DNA methyltransferase; EAT, epicardial adipose tissue; ECM, extracellular matrix; HAT, histone acetyltransferase; HDAC, histone deacetylase; HMT, histone methyltransferase; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; ncRNAs, noncoding RNAs.

ischemia-reperfusion injury and expression of proinflammatory cytokines [54]. In a recent study, SAHA was also reported to attenuate Takotsubo-like myocardial injury by targeting an epigenetic Ac/Dc axis [55].

An emerging and promising class of epigenetic drugs is represented by the bromodomain and extra-terminal motif (BET) inhibitors. These drugs can reversibly bind the bromodomains of BET proteins BRD2, BRD3, BRD4, and BRDT and inhibit the interaction between acetylated residues and transcription factors. JQ1, a novel BET inhibitor, was shown to protect against pressure overload hypertrophy and HF in mice [56]. Unbiased tran-scriptomics studies found that BET inhibition is mainly associated with suppression of NFκBand TGFβ, two central pathways underlying HF [56]. Along the same line, the BET inhibitor Apabetalone (RVX-208) was shown to prevent endothelial inflammation (IL-6 and TNF-α) [57,58] and diabetic hindlimb ischemia by epigenetic regulation of the angiogenesis inhibitor thrombospondin-1 (THBS1) [59].

A recent phase III clinical trial, BETonMACE, was designed to investigate the effects of Apabetalone on cardiovascular outcome in more than 2000 patients with diabetes and a recent acute coronary

syndrome. Although the trial failed in meeting its primary endpoint, the drug was associated with a reduced risk of first and recurrent HF hospitalization [60▪]. A recent subanalysis of BETonMACE recently showed that the Apabetalone could be particularly effective in preventing HF-related events among diabetic patients with chronic kidney disease. Although these data are encouraging, larger clinical trials are be needed to prove the efficacy of Apabetalone in patients with HFpEF and HFrEF.

Therapeutic modulation of microRNAs is also emerging as an effective strategy in HF patients. Remlarsen, a miR-29 mimic with powerful antifibrotic activity, has recently completed Phase II in a clinical trial designed to investigate the effects on preventing or reducing keloid formation in subjects with a history of keloid scars. These results pave the way for the application of Remlarsen in HF, given the pivotal role of fibrosis in this setting [16▪]. New targeting approaches are also being developed against miR-21, miR-155, and miR-33, with the aim of tackling fibrosis [61]. In line with these results, CDR132L, a synthetic lead-optimized oligonucleotide inhibitor of miR-132, reported preclinical efficacy and safety in animal studies. Indeed, CDR132L was effective in reducing diastolic dysfunction as well as left atrial size and remodeling [62]. Of clinical relevance, a phase 1b randomized, double-blind, placebo-controlled study recently showed that miR-132 inhibition determined a sustained miR-132 reduction in plasma and was well tolerated [63]. Of note, administration of CDR132L ($\geq$1 mg/kg) displayed a median 23.3% NT-proBNP reduction, vs. a 0.9% median increase in the control group [$P = 0.2519$, Fisher's exact test; odds ratio: 2.9167 (95% CI: 0.5938–14.3270)]. Furthermore, CDR132L treatment induced significant QRS narrowing and encouraging positive trends for relevant cardiac fibrosis biomarkers [63].

Due to their chemical structure, which makes them successful methyl donors, folates can be considered epigenetic drugs able to modulate DNA-methylation status and gene expression. Though only a few studies are made in this area, the methyl group donated by this class influences CpG methylation pattern on specific gene loci and chromatin architecture thus favoring detrimental transcrip-tional programs involved in HFpEF development [64]. Dietary supplementation with methyl donors was reported to increase p16 promoter DNA meth-ylation thus preventing vascular senescence and neointima formation [65,66]. Other DNA-methylation agents are known for their potential use in vascular diseases. For example, 5′-azacytidine (Vidaza), a chemical analog of cytidine, was identified as a DNA methyltransferase inhibitor able to foster vascular repair and endothelial differentiation by inducing hypomethylation of eNOS promoter [44]. The latter mechanisms (vascular aging and impaired eNOS signaling) can be relevant in patients with HFpEF, as it may contribute to rescuing microvascular dysfunction [67,68].

Moreover, widely used drugs, such as metformin, SGLT-2 inhibitors, and statins, have shown indirect effects on the epigenome and can therefore be considered as potential therapeutic tools to edit epigenetic signals in patients with HFpEF and/or HFrEF [69–71].

CONCLUSION

Although epidrugs represent an interesting approach for the treatment of CVD, we are still far from having developed selective approaches tackling epigenetic signals in specific cells. Most of the epigenetic drugs lack specificity and can therefore affect several signaling pathways leading to undesirable side effects. However, the recent BETon-MACE trial with Apabetalone did not show relevant side effects with this class of drugs. Inhibition of proteins able to read chromatin marks, such as BET proteins, is indeed one of the next frontiers of pharmaceutical research in clinical cardiology. Future clinical trials will help to elucidate the potential of BET inhibition in the setting of HF. The application of epigenetic information as a diagnostic tool also represents an attractive challenge in the decades to come [18]. In this context, epigenetic changes are rather unique as they reflect the contribution of environmental factors during the course of life. Given the recent explosion of environmental cardiology [72], epigenetics can help answer complex biological questions and may offer powerful readouts to be employed for an early diagnosis of HFpEF [72]. The implementation of computational epigenetics on large epigenomic datasets can lead to a scrutiny assessment of the epigenetic landscape and contribute to developing personalized approaches for the management of cardiovascular patients. Larger cohort studies and clinical trials are needed to better delineate the contribution of clini-calepigenetics in the setting of CVD and HFpEF [11].

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