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Epigenetics and obesity cardiomyopathy: From pathophysiology to prevention and management

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ABSTRACT

Uncorrected obesity has been associated with cardiac hypertrophy and contractile dysfunction. Several mechanisms for this cardiomyopathy have been identified, including oxidative stress, autophagy, adrenergic and renin–angiotensin aldosterone overflow. Another process that may regulate effects of obesity is epigenetics, which refers to the heritable alterations in gene expression or cellular phenotype that are not encoded on the DNA sequence. Advances in epigenome profiling have greatly improved the understanding of the epigenome in obesity, where environmental exposures during early life result in an increased health risk later on in life. Several mechanisms, including histone modification, DNA methylation and non-coding RNAs, have been reported in obesity and can cause transcriptional suppression or activation, depending on the location within the gene, contributing to obesity-induced complications. Through epigenetic modifications, the fetus may be prone to detrimental insults, leading to cardiac sequelae later in life. Important links between epigenetics and obesity include nutrition, exercise, adiposity, inflammation, insulin sensitivity and hepatic steatosis. Genome-wide studies have identified altered DNA methylation patterns in pancreatic islets, skeletal muscle and adipose tissues from obese subjects compared with non-obese controls. In addition, aging and intrauterine environment are associated with differential DNA methylation. Given the intense research on the molecular mechanisms of the etiology of obesity and its complications, this review will provide insights into the current understanding of epigenetics and pharmacological and non-pharmacological (such as exercise) interventions targeting epigenetics as they relate to treatment of obesity and its complications. Particular focus will be on DNA methylation, histone modification and non-coding RNAs.

Contents

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1. Introduction

1.1. Obesity and organ complications, cardiomyopathy: general health impact

Obesity, a disorder originated from interplays between genetic and environmental factors such as lifestyle, culture, physiology and behavior, is reaching pandemic proportions in the 21st century and imposes severe health challenges and economic burdens worldwide (Bhaskaran et al., 2014; Van Gaal & Maggioni, 2014; Burgio et al., 2015; Chang & Neu, 2015; Sharma et al., 2015). According to the World Health Organization (WHO), the prevalence of obesity has doubled worldwide since 1980 (Keating et al., 2014; Morgen & Sorensen, 2014; Ng et al., 2014). More alarmingly, childhood obesity has risen dramatically over the past decades with more obese and overweight children becoming overweight adolescents and adults (Daniels et al., 2005; Daniels et al., 2009; Nadeau et al., 2011; Chesi & Grant, 2015; Simmonds et al., 2015; Sperling et al., 2015). From an economic perspective, obesity and its comorbidities have imposed high medical costs, loss of daily productivity and risk of premature death (Morgen & Sorensen, 2014; Ng et al., 2014; Cordero et al., 2015). This metabolic disorder is believed to be originated from a disturbed balance between caloric intake and energy expenditure, resulting in excess body fat and development of a cluster of adverse chronic disorders including the overall cardiovascular diseases, hypertension, hyperinsulinemia, glucose intolerance, dyslipidemia, type 2 diabetes mellitus, non-alcoholic fatty liver diseases (NAFLD), cancer, sleep dyspnea, musculoskeletal disorders, Alzheimer's disease, kidney and pulmonary diseases (Poirier et al., 2006; Bhaskaran et al., 2014; Cavalera et al., 2014; Van Gaal & Maggioni, 2014; Elia & Condorelli, 2015).

Pathogenesis for obesity is complex and multifactorial including genetic, behavioral, and environmental factors (Morgen & Sorensen, 2014; Chang & Neu, 2015). It is generally believed that gene–environment interactions may be responsible for the modification of gene expression and epigenetic mechanisms, leading to obesity and associated complications (Chang & Neu, 2015; Cordero et al., 2015; Kotsis et al., 2015). Moreover, mounting evidence from epidemiological and experimental studies has suggested a theory of "fetal programming of adult disease" for obesity and associated metabolic complications, denoting the essential role for intrauterine and early postnatal environment (Gali Ramamoorthy et al., 2015; Thornburg, 2015). In particular, both under- and over-nutrition during intrauterine and early postnatal stages profoundly affects human health later on in life. Current long-term treatment of obesity mainly works through reducing energy intake, increasing satiety, decreasing hunger, reducing absorption of calories, and pharmacotherapy, in conjunction with appropriate healthy educational interventions (Wharton, 2015). In severe cases, application of intra-gastric balloon insertion, shock therapies and bariatric surgery should be considered (Nair & Ren, 2009; Cordero et al., 2015; Wharton, 2015). Nonetheless, the existence of a knowledge gap for the potential interplay among genetic and non-genetic factors (such as nutrition and environmental exposure) in the pathogenesis of obesity has largely hindered the efficacy and outcome of anti-obesity therapy.

This review aims to discuss the current understanding of genetic and epigenetic origins of obesity and associated complications, with a goal to provide a stepping stone for future, better designed studies on anti-obesity therapy targeting on either genetic or epigenetic origins of the disease. We will also briefly discuss the contribution of early life nutrient factors, including preconception, intrauterine and postnatal nutrition and energy, in transgenerational programming, and prevalence of obesity and chronic metabolic diseases later on in life (Wahlqvist et al., 2015).

Obesity is known to trigger a cluster of inter-correlated risk factors including lipid, glucose and blood pressure anomalies for cardiovascular diseases including hypertension, atherosclerosis, diabetes mellitus, left ventricular hypertrophy, heart failure, atrial fibrillation and stroke (Bonow & Eckel, 2003; Poirier et al., 2006; Nadeau et al., 2011; Van Gaal & Maggioni, 2014; Ayer et al., 2015; Mahajan et al., 2015; Ren & Anversa, 2015). The broad spectrum of obesity-related risk factors for cardiovascular diseases has been summarized into a few categories (Fig. 1) while retaining the variance for the original variables (Goodman et al., 2005; Ayer et al., 2015). In an exploratory factor analysis (principal components analysis) involving 1578 adolescents, four uncorrelated summary factors have been patterned as the main cardiovascular risk factors: cholesterol (including LDL and free cholesterol), carbohydrate-metabolic (including glucose, insulin, HDL-cholesterol, triglycerides), adiposity [including body mass index (BMI), and waist circumference], and blood pressure (Goodman et al., 2005). This statistical technique seems to represent a valid avenue to evaluate the underlying determinants of cardiovascular disease risk in uncorrected obesity. In the past decades, clinical and experimental evidence showed that obesity is an independent risk factor for coronary heart diseases, in particular heart failure (Kenchaiah et al., 2002; Kenchaiah et al., 2009; Li et al., 2012; Zhang et al., 2012; Guo et al., 2013; Gupta et al., 2015; Ren & Zhang, 2015). The unfavorable effects of obesity on blood pressure, dyslipidemia and glucose levels, three major risk factors associated with obesity, are believed to account for 45%–50% of increased cardiovascular outcomes, in particular coronary heart diseases (Van Gaal & Maggioni, 2014). This is supported by the positive clinical outcome of reduction in blood pressure, glucose and lipid (e.g., statins), as well as lifestyle modification in the clinically relevant improvement of cardiovascular function (Van Gaal & Maggioni, 2014).

Uncorrected obesity is closely linked to cardiac remodeling accompanied by structural and functional abnormalities (Bonow & Eckel, 2003; Eckel, 2008). Increased left ventricular (LV) mass is seen in obese individuals displaying a positive correlation with BMI (Sivanandam et al., 2006). Interestingly, the strength in the association between LV mass and BMI rises with biological age (Sivanandam et al., 2006). Other evidence has depicted a major role for childhood obesity in cardiac structure and cardiac remodeling later in adulthood (Ayer et al., 2015). Currently, the mechanisms contributing to these culprit remodeling alterations remain somewhat elusive for obesity although a complex interplay of hemodynamic, neurohormonal, and metabolic factors seems to contribute to oxidative stress, inflammation, apoptosis, dysregulated autophagy, hypertrophy, interstitial fibrosis, lipotoxicity, adrenergic and renin–angiotensin aldosterone overflow as well as metabolic defects in obese hearts (Ren & Kelley, 2009; Zhang & Ren, 2011; Zhang et al., 2013a, 2013b; Cavalera et al., 2014; Dong & Ren, 2014; Liang et al., 2015; Mahajan et al., 2015). Recent studies have highlighted the role of dysfunctional visceral adipose tissue (VAT) in inflammation, oxidative stress, and angiogenesis contributing to myocardial abnormalities in obesity (Fig. 1). A growing body of evidence has depicted a pivotal role for these mediators, known as adipocytokines such as adiponectin, leptin, resistin, interleukins and tumor necrosis factor-α (TNF-α), in the onset and development of cardiovascular diseases through an autocrine, paracrine or a distant endocrine fashion (Ayer et al., 2015).

The term "cardiomyopathy of obesity" was derived mainly based on cardiac functional, morphological, and metabolic abnormalities due to obesity alone, with specific attention to the underlying signaling pathways in increased adiposity (Kasper et al., 1992; Alpert, 2001a, 2001b; Owan & Litwin, 2007). Besides heart failure, atrial fibrillation is another morbidity factor usually associated with obesity. Epidemiological evidence has indicated that weight loss may greatly reduce atrial fibrillation burden and atrial fibrillation recurrence following pharmacological treatment (Nalliah et al., 2015). Regardless of structure remodeling or electronic remodeling, uncorrected obesity plays an important role in the process of cardiac hypertrophy and contractile dysfunction (Bonow & Eckel, 2003; Cavalera et al., 2014; Burgio et al., 2015). In addition to adiposity, concomitant conditions often present in obese individuals such as hypertension, sleep apnea, and diabetes mellitus

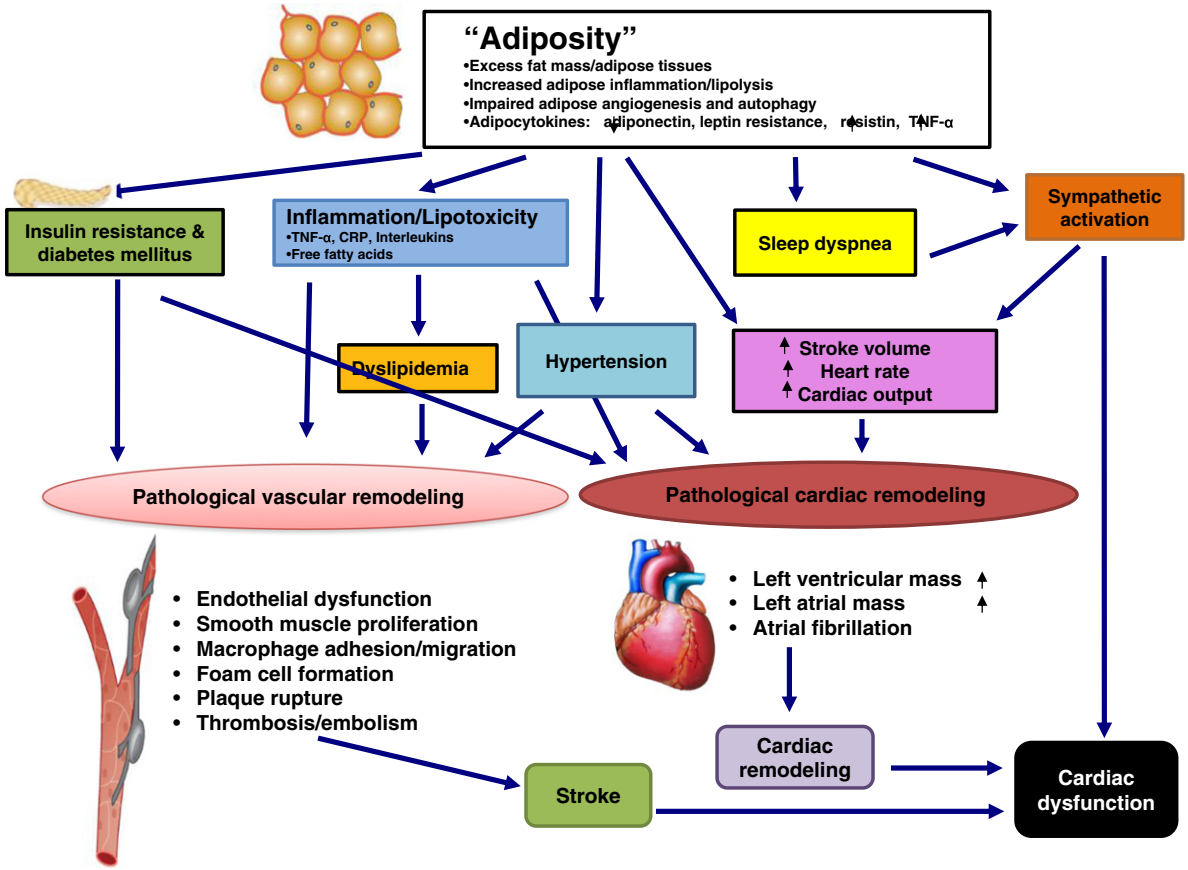

Fig. 1. Schematic diagram displaying various contributing factors involved in the complex pathophysiology of complications in particular heart dysfunction in the "adiposity" of obesity. CRP: C reactive peptide; TNF-α: tumor necrosis factor α; [adapted from (Ayer et al., 2015) with modifications].

may also compromise heart geometry and function (Mahajan et al., 2015; Nilsson et al., 2015). In addition, differences in nutrition, gut microbiota, and exercise are essential to the occurrence of cardiovascular complications in obesity (Hardy et al., 2012; Kotsis et al., 2015; Lavallard et al., 2012). It should be mentioned that establishing a clear link between obesity and heart failure may be complicated because obesity needs to be present for years prior to the appearance of cardiac risk. No longitudinal examination has been done for changes in cardiac size and function in obese humans, which makes it somewhat uncertain with regards to the true "cardiomyopathy of obesity" (Owan & Litwin, 2007). Moreover, the overweight and obese patients are typically poorly treated for these comorbidities (blood pressure, lipid and glucose abnormalities) because of medical inertia and the believe or hope by many physicians that weight loss alone would suffice. Nonetheless, new and novel mechanisms for obesity associated heart failure including genetic and epigenetic pathways have been recently described.

Several studies have revealed that overweight or obesity is tied with a better survival rate in patients with cardiovascular disease (Alpert et al., 2016; Kim et al., 2015; Sharma et al., 2015). The risk for total mortality and cardiovascular mortality and hospitalization appears to be the highest in patients with heart failure who were underweight as defined by low BMI, whereas the overall risk for cardiovascular mortality and hospitalization appears to be the lowest in overweight subjects (Sharma et al., 2015). The particular epidemiology of heart failure suggests that obesity is associated with better prognosis in patients with heart failure (Lavie et al., 2014). This is the so-called obesity paradox. Moreover, the obesity paradox exists after percutaneous coronary intervention (PCI) with a significantly lower mortality in overweight and obese patients compared with normal weight patients (Bundhun et al., 2015). It is suggested that the obesity paradox may be partially due to an overestimation of the severity of heart failure in obese patients due to presence of multiple factors such as dyspnea (Stokes & Preston, 2015). In addition, obesity is a product of biases involving reverse causation and is confounded by other risk factors including smoking. It appears that obesity would lose its protective effect following adjustment for the typical prognostic indices of heart failure (Pozzo et al., 2015). Most of the current available data pertaining to the "obesity paradox" uses BMI as the gold standard to define obesity although the reliability of the BMI measure is being challenged. Other measures of body fat and body composition are getting recognized including waist circumference, waist-to-hip ratio, skinfold thickness, and bioelectrical impedance of body composition (Gupta et al., 2015). Although weight loss has proven to improve cardiac structure and function as well as alleviate symptoms in heart failure, large scale studies are still lacking on the impact of weight loss on clinical events in heart failure, thus making it somewhat difficult for definitive guidelines on optimal body composition in patients with heart failure (Lavie et al., 2016).

1.2. Epigenetics and human diseases

The advance of biomedical research has greatly enriched our contemporary understanding of genetic variants in determination of anthropometric parameters and human diseases. However, monozygotic twin pairs, with essentially similar genetic variants and environments before and immediately after birth, display phenotypic discordance for a wide range of traits including body mass and adiposity. Differences in functional complexity of genomes at the epigenetic level are believed to account for such discordances for monozygotic twins including adiposity and disease prevalence (Haggarty, 2015). Epigenetic modulation develops in response to a wide range of genetic and non-genetic factors such as fitness, age, diet, energy expenditure, social status and environmental insults (Haggarty, 2015; Martinez-Jimenez & Sandoval, 2015;

Whayne, 2015). Epigenetics, originally coined by Conrad Waddington in the 1940s, is referred to as cellular and physiological heritable (mitotic or meiotic) phenotypical variations elicited by environmental factors independent of the genomic DNA sequence (Slack, 2002), as shown in Fig. 2. Epigenetics contributes to disease traits and phenotypes independent of the intrinsic genome coding (Dick et al., 2014; Osorio, 2014). The period around conception is highly susceptible to environmental influences as evidenced by epigenetic imprinting in offspring (Haggarty, 2015). The epigenetic processes include chromatin remodeling, DNA methylation, histone modification, and non-coding RNAs (ncRNAs) regulation, resulting in either transcriptional suppression or activation independently of the DNA genome sequence. Epigenetic status may be also affected by genetic polymorphisms in DNA processing enzymes including DNA methyltransferase, methylcytosine dioxygenase, and methylene tetrahydrofolate reductase (Haggarty, 2015). Given the unique role of epigenetics in linking environmental influences to the human genome, the field has received a lot of attention in recent years with epigenetics bridging early life exposures to later adult health conditions (Haggarty, 2015). Several international initiatives have been launched to address epigenetics in the regulation of human health and disease, including the International Human Epigenome Consortium (IHEC) and Human Epigenome Project (HEP) (Abbott, 2010; American Association for Cancer Research Human Epigenome Task & European Union, 2008).

Over the last several years, epigenetics has emerged as an essential path through which the environment is capable of modulating the human genome that may persist over decades, or even more than one life course or generation (Haggarty, 2015). The tissue-specific gene expression pattern is governed by chromatin modifications (DNA methylation, histone modifications) and RNA interactions (ncRNA). In eukaryotes, the genome is located in the nucleus in the form of chromatin — a DNA–protein complex with DNA packed around histone proteins, in building units or blocks commonly referred to as nucleosomes. A nucleosome represents 147 base pairs of DNA looped around an octomeric histone core consisting of two H3–H4 histone dimers surrounded by two H2A–H2B dimers. The nucleosomes are threaded together by a linker histone H1 for stability of packaged structures. Changes in the chromatin structure alter gene expression transcriptionally whereas ncRNAs affect gene expression at posttranscriptional levels (Ungerer et al., 2013). These effects on gene expression impose major consequences for development and well-being across the life course and are involved in the pathogenesis of human diseases including tumor, inflammation, metabolic disorders and cardiovascular diseases (Brazel & Vernimmen, 2016; Keating & El-Osta, 2015; Ozanne, 2015; Ramachandran et al., 2015). Both DNA and protein contents in nucleosome structures may be modified, leading to alteration of chromatin conformation and accessibility. The methyl and acetyl groups function as the epigenetic marks denoting epigenetic status. DNA methylation is accomplished by DNA methyltransferases (DNMTs) to covalently anchor a methyl (CH_3) group to a DNA nucleotide [e.g., cytosine (C) to form 5-methylcytosine (5mC)]. Methylation usually attacks C nucleotide over the guanine (G) nucleotide.

Four main variants of DNMTs are found in humans, namely DNMT1, DNMT3A, DNMT3B and DNMT3L, to mediate methylation. DNMT1 serves to maintain the existing methylation patterns. DNMT3A and DNMT3B, on the other hand, regulate de novo methylation, while DNMT3L functions as a unique co-factor in the methylation of gamete imprints (Haggarty, 2015). In general, DNA methylation promotes condensation of chromatin structure, leading to the silence or suppression of gene expression as the DNA cannot be accessed for transcription. DNA methylation can be removed by active demethylation using the ten-eleven translocation (TET) methylcytosine dioxygenase enzymes to turn methyl-C into hydroxymethyl-C. The memory stored by methyl-C is usually erased during cell division because hydroxymethyl-C is not recognizable by DNMT1 (Haggarty, 2015).

Histones, on the other hand, make up the nucleosome core. Histone proteins contain long N-terminal tails protruding from nucleosomes. These unstructured tails are usually subject to post-translational modification (e.g., phosphorylation, acetylation, methylation, ubiquitination, ADP-ribosylation and sumoylation), which are deemed dynamically reversible. DNA methylation and histone modification may influence chromatin structure and subsequently gene regulation. It is noteworthy that various epigenetic modifications associated with different states of gene expression and chromatin structure may be faithfully propagated

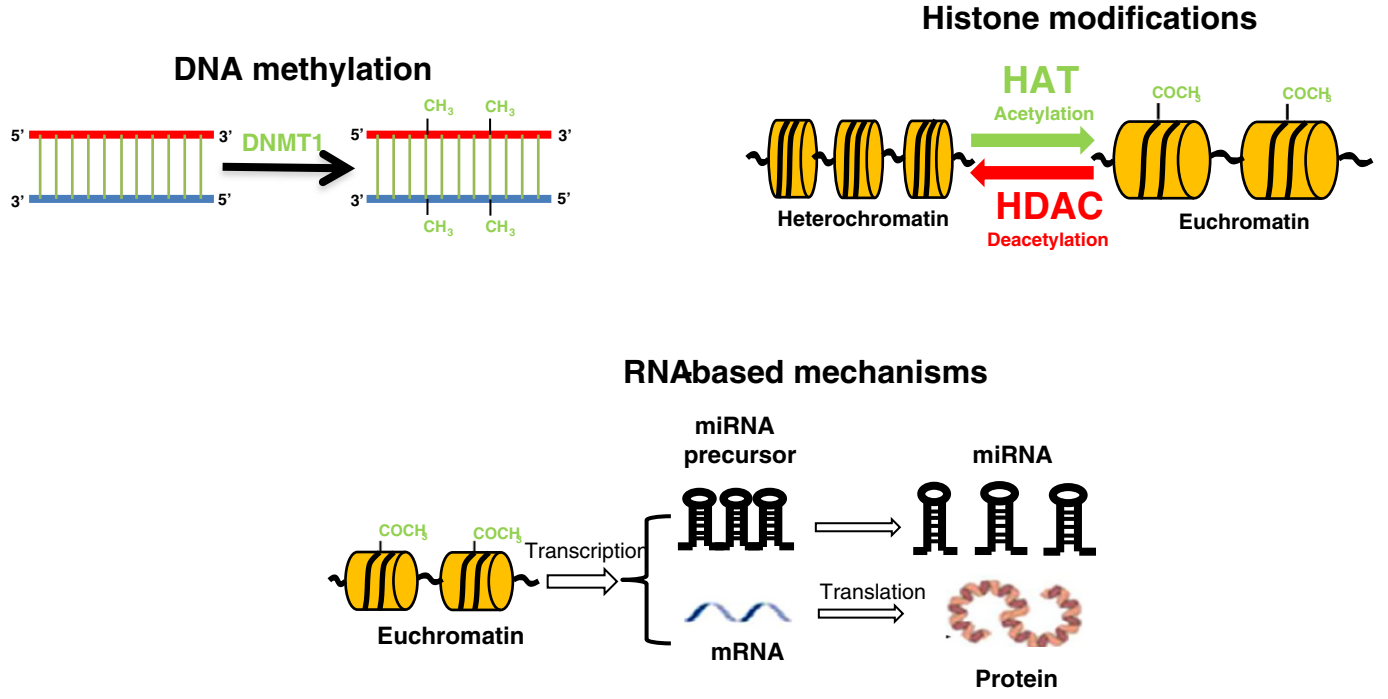

Fig. 2. Main epigenetic machineries, including DNA methylation (e.g., cytosine methylation), histone alterations, and RNA-based transcriptional control, which may alter the cellular gene expression profile and phenotype under both physiological and pathophysiological settings.

during cell divisions through coupling with the DNA replication process. Such a propagation process of epigenetic information is controlled by methyl-binding proteins, transcription factors, and protein insulators, including methyl CpG binding protein 2 (MeCp2), and CCCTC-binding factor (CTCF). The methyl-CpG-binding protein family is considered the "readers of the epigenome" as these proteins recruit histone deacetylases and methylases as well as chromatin remodelers to methylated DNA segments associated with gene repression (Du et al., 2015). On the other hand, CTCF serves as a protein insulator to regulate intra- and inter-chromosomal configuration, DNA methylation as well as global chromatin organization and remodeling, contributing to the repression or activation of gene transcription (Franco et al., 2014; Haggarty, 2015).

Ample evidence has suggested that the risk of chronic diseases depends on epigenetic control by early life environmental cues (developmental programming). Similar to the human Dutch Hunger Winter famine case during World War II, environmental exposure to factors including nutritional, psychological, and social stress, toxins and substance abuse in early life may serve as triggers for epigenetic programming for various comorbidities later (Vaiserman, 2015a, 2015b). In mammals, the epigenome may be subject to major epigenetic modifications during gametogenesis and early embryogenesis (Messerschmidt et al., 2014; Vaiserman, 2015a, 2015b). In the early embryo, methylation levels are minimal to allow removal of gamete-specific methylation inherited from parents for the purpose of pluripotency. Following implantation, a surge of de novo methylation develops followed by a new demethylation–remethylation cycle in the primordial germ cells (embryonic progenitors of oocytes and sperm). Nonetheless, such epigenetic event shows distinct patterns between primordial germ cells and embryos. Demethylation process is considered near complete in primordial germ cells, whereas methylation of imprinted regions is protected in early embryos, thus allowing expression of specific parent-of-origin genes in early embryos (Messerschmidt et al., 2014). Therefore, epigenetic modifications elicited by environmental influences during these critical periods pertain across the life course, possibly resulting in unfavorable consequences in adulthood (Messerschmidt et al., 2014; Vaiserman, 2015a, 2015b).

The link between epigenetic regulators and adverse early life events in later health consequences has been substantiated by epigenome-wide association studies (EWAS) and work dealing with specific candidate genes. One main mechanism in associating various factors such as nutrients, physical activity, dietary factors, substance abuse, and environmental toxins to epigenetic control of gene expression is through metabolites that may function as cofactors and allosteric regulators for epigenetic processes. Transcriptional regulators may be present to sense levels of intermediary metabolites tied to biological processes including heritable, long-term imprinting and DNA methylation. Moreover, the heritability of epigenetic traits is believed to add to the complexity where the inherited epigenetic modifications may require a revisit of pathogenesis of human obesity and metabolic diseases (Martinez-Jimenez & Sandoval, 2015; Whayne, 2015). Epigenetic machinery has been extensively examined in recent studies in cancer, inflammation, diabetes mellitus, autoimmune, neurological and imprinting disorders, and advanced aging (Castillo-Fernandez et al., 2014; Lardenoije et al., 2015). Furthermore, epigenetics associated with cholesterol, lipid and glucose homeostasis have been shown to play a major role in the susceptibility, development and progression of complex morbidities such as type 2 diabetes mellitus, obesity, metabolic syndrome, and non-alcoholic fatty liver disease.

Imprinting disorders, a group of rare, underdiagnosed congenital diseases, are characterized by alterations in the imprinted chromosomal segments and genes, i.e., parent-of-origin specific genes. Each imprinting disorder is characterized by unique clinical features associated with specific imprinting defects for development, growth and metabolism. The diverse imprinting disorders share common features, not only in molecular mechanisms, but also in outcomes of development, growth and metabolism (Eggermann et al., 2015a, 2015b). Not surprisingly, a systematic analysis of imprinting disorders should help not only to reveal mechanisms behind epigenetic changes in health and disease, but also to guide personalization of diagnosis and treatment from the perspective of precision medicine. In this review, we will discuss the current understanding for the role of epigenetic mechanisms (DNA methylation, histone modification and ncRNA) in obesogenesis and associated cardiac complications, and their translational potential to reveal novel therapeutic remedies.

2. Epigenetics versus genetics in the regulation of heart homeostasis

Epigenetics is involved in nearly all disease processes including cardiovascular disease, in particular heart diseases. Cardiovascular diseases are a group of complex, multigenic anomalies resulting from both genetic and epigenetic factors. A long-perceived paradigm is that the primary determinant of cardiovascular diseases resides within the stable DNA sequence of our genes. The DNA code is identical across all cell types in the body and can be transmitted unaltered in mitosis and meiosis. A range of 40% to 80% of cardiovascular diseases may be attributed to genetic factors (Webster et al., 2013). However, this genetic paradigm is challenged given the role for epigenetics in the control of not only cardiovascular homeostasis but also disease inheritability (Handy et al., 2011; Schones et al., 2015; Whayne, 2015; Yan & Marsden, 2015). Changes in ncRNA, DNA methylation patterns and histone structure have been shown to govern cardiovascular disease vulnerabilities (Thornburg, 2015), supporting the developmental origins of disease concept put forward by Prof. David Barker (Barker, 2004; Barker & Thornburg, 2013). It is noteworthy that epigenetic modifications are reversible, and vary among different cell types or in response to environments. Findings from these reports should shed some light towards reversing or preventing detrimental epigenetic outcome or "memory" for cardiovascular diseases. Moreover, in vitro and in vivo studies have suggested that prenatal protein restriction and fetal malnutrition directly modify the levels of specific genes, predisposing the adult to the onset of overall cardiovascular diseases (Portela & Esteller, 2010; Schiano et al., 2015). More importantly, these epigenetic marks may get transmitted to the next generation. The field of epigenetics has experienced a remarkable growth and perhaps an explosion over the past years with novel concepts and advances in cell biology and epigenomic technologies. The epigenetic paradigm in the etiology and progression of human disease has been pervasive throughout genomic and non-genomic science, clinical medicine, epidemiology and popular culture (Babbitt et al., 2016; Kurdyukov & Bullock, 2016).

Local alterations in DNA methylation and chromatin architecture have been suggested to affect specific transcriptional machineries to trigger cardiac pathologies in the adult life. The interplay between genetics and epigenetic factors such as environments and nutrients has been depicted to regulate the susceptibility for cardiovascular disease, obesity, metabolic syndrome, and diabetes mellitus (Haas et al., 2013). This is evident by overt epigenetic modifications in cardiovascular anomalies including coronary heart disease, hypertension, peripheral vascular disease and stroke in the presence of major pro-epigenetic cardiovascular risk factors such as aging, high fat/caloric intake, exercise, drinking and tobacco abuse (Whayne, 2015). In addition, prevalence of cardiovascular diseases in adulthood is tightly controlled by early developmental factors such as gene imprinting, amniotic sac development, maternal and fetal nutritional status, among others (Horvath et al., 2014; Singhal et al., 2015; Thornburg, 2015). Through these epigenetic modifications, there may be infinite developmental cardiovascular benefit/harm for the fetus and newborn later on in adult life health status. In addition, maternal influences such as diet, body composition, stress and exercise may also contribute to the phenotype in offspring (Whayne, 2015). Exposure to a hostile environment such as aging, over/mal nutrition as well as alcohol, drug and tobacco exposure during early developmental stage could result in various cardiovascular

pathologies, whereas beneficial calorie restriction promotes longevity by favorably modulating epigenetic mechanisms such as DNA methylation and histone modification (Sargent, 2015). It is perceived that histone modifications and chromatin remodeling regulate adaptive as well as maladaptive cardiovascular events such as cardiac hypertrophy and failure (Montgomery et al., 2007). On the other hand, DNA methylation is believed responsible for the gene promoter methylation and hypermutability of cardiac genes (Meurs & Kuan, 2010). Altered methylation patterns and extent of target genes are known to correlate with heart failure, as evidenced by the genome-wide DNA methylation analysis of human hearts, which revealed significantly lowered global promoter methylation for genes associated with heart failure (Cao et al., 2014; Marin-Garcia & Akhmedov, 2015). Hypomethylation of long interspersed nucleotide elements was also evident in elderly patients with ischemic heart diseases (Cao et al., 2014; Webster et al., 2013).

Several studies have demonstrated a key role for epigenetic regulatory mechanisms in cardiac homeostasis, in particular under pathological stress and injury. Given that adult cardiomyocytes are terminally differentiated with limited proliferative capacity, epigenetic regulation may modulate adaptive and reversible hypertrophy to meet the higher hemodynamic requirements in response to physiological stimuli (Udali et al., 2013). A number of histone-modifying and chromatin remodeling enzymes as well as ncRNAs are demonstrated to have essential roles in cardiac development and function, while their dysregulation along with the complex interplay with genetic mechanisms promote the onset and development of pathological changes in the heart (Marin-Garcia & Akhmedov, 2015). Adaptive cardiac hypertrophy turns out to be maladaptive and irreversible under pathological conditions such as myocardial infarction, obesity, hypertension, aging and diabetes (Marin-Garcia & Akhmedov, 2015). Pathological cardiac hypertrophy is associated with dramatic alterations in genetic and epigenetic signaling associated with contractile apparatus and metabolism, resulting in cardiac hypertrophy and heart failure (Schiano et al., 2015). Specific cardiac pathologies associated with obesity and their possible link to epigenetics will be briefly discussed in the following sections.

3. Role of deoxyribonucleic acid methylation in obesogenesis and cardiomyopathy

The current epidemic of obesity demands for a better understanding behind the mechanisms through which genetics and epigenetic factors interact to determine metabolic traits. Epigenetic states are dynamic, potentially reversible marks, and may be influenced by genetics, environment, and stochastic events attributing to the ultimate phenotypic variations (Castillo-Fernandez et al., 2014). DNA methylation, a biochemical reaction of adding a methyl group to the cytosine or adenine dinucleotide sites in the genome named CpG islands using DNA methyl transferase, refers to a unique mechanism through which early-life modifications are biologically memorized or embedded (Demetriou et al., 2015). Abnormal DNA methylation or demethylation at the specific gene promoter regions is implicated in genomic imprinting and development of human diseases including obesity and cardiovascular diseases (Yara et al., 2015).

Using the Sequenom MassARRAY technique, Godfrey and colleagues examined the methylation status of 68 CpGs 5′ from five candidate genes in healthy neonatal umbilical cords. Their findings revealed altered methylation at particular CpGs (including 31 CpGs with median methylation ≥5% and a 5–95% range ≥10%). These methylation changes seemed to be related to maternal diet during pregnancy and child adiposity at 9 years of age, suggesting the utility in perinatal epigenetic status in evaluating individual vulnerability to obesity and metabolic disease later on in life (Godfrey et al., 2011). In another work, increased BMI was found to be associated with a rather pronounced methylation at the HIF3A locus in adipose tissues and blood cells (Dick et al., 2014). Likewise, higher DNA methylation status at three HIF3A CpGs seems to be tied to increased weight and adiposity in infants (Pan et al., 2015) although no prenatal factor was found to be responsible for HIF3A hypermethylation. Seven SNPs that are associated with obesity traits are accompanied by DNA methylation in white blood cells, subsequently affecting adiposity and weight reduction in obese individuals. Differential DNA methylation statuses were noted in all of the CpG-SNPs examined. Interaction between epigenetic (allele-specific methylation) and genetic components in CpG-SNPs, such as in BDNF and SH2B1 genes, suggests a possible role for these SNPs in obesity as they contribute to a lower body weight reduction.

Methylation levels of fat mass and obesity-associated (FTO) and BDNF seemed to be tied to body weight and body weight gain. Moreover, the rs7359397 (SH2B1) site is closely correlated with BMI, body weight, and truncal fat mass (Mansego et al., 2015). DNA methylation of the essential regulator of lipid metabolism fatty acid binding protein 3 was also linked with traits of metabolic syndrome in 517 individuals from 40 families (Zhang et al., 2013a). In addition, methylation patterns of three clock genes participating in circadian rhythm (*CLOCK*, *BMAL1* and *PER2*) were found to be associated with anthropometric traits such as BMI and adiposity (Milagro et al., 2012). Besides modifying gene expression governing obesity traits, DNA methylation may also alter various environmental cues to obesity as obesity is a programmable disease under epigenetic modifications when exposed to unfavorable environmental insults such as oxidative stress, fat diet, alcohol, and air pollution. Consistent with this notion, perturbation of the redox-sensitive hypoxia inducible transcription factor (HIF) signaling has been found to be pivotal in the regulation of weight gain. Oxidative stress may be coordinated with changes in methylation patterns, leading to the chronic disease state of obesity (Yara et al., 2015). In a more recent study, compromised oocyte meiotic maturation, spindle morphology, and oocyte polarity were noted in high fat diet-induced and gene mutation-induced obesity (ob/ob) in association with overt oxidative stress, mitochondrial injury and early apoptosis. DNA methylation and histone methylation (as manifested by levels of 5 mC, H3K9 and H3K27 methylation) were altered in oocytes from obese mice, suggesting a role for epigenetic modifications and oxidative stress-induced early apoptosis in reduced oocyte quality in obesity (Hou et al., 2016).

Early-life adversity predisposes cardiometabolic disease risk during later life or subsequent generations. Early-life environmental exposures disturb epigenetic programming in the brain and heart, resulting in changes in gene expression, heart function and behavior. Changes in DNA methylation have been noted in peripheral blood of psychiatric patients, raising an issue whether circulating markers reflect similar epigenetic changes in the brain (Kundakovic et al., 2015). In utero exposure to bisphenol A (BPA), an endocrine disruptor for environmental exposure resulting in a ubiquitous trait of obesity and cardiovascular diseases, was found to induce DNA methylation in the transcriptional region of the BDNF gene in mice, in a manner reminiscent of human subjects exposed to high maternal BPA levels in utero (Kundakovic et al., 2015). BPA also triggered DNA methylation and transgenerational inheritance of heart disorder (heart failure) associated with depressed insulin receptor signaling (Lombo et al., 2015). These findings indicated that blood DNA methylation may serve as a predictor or an early biomarker for BDNF-associated psychiatric disorders as a result of early-life adversity such as autism, depression, schizophrenia, and bipolar disorder.

Although convincing evidence is still lacking with regards to DNA methylation in obesity cardiomyopathy, a number of reports have consolidated the role of DNA methylation in heart diseases, in particular heart failure (Greco & Condorelli, 2015; Kao et al., 2014; Voelter-Mahlknecht, 2016). DNA methylation at CpGs of promoters and gene bodies displays a distinct profile between myopathic (such as failing or hypertrophic) and healthy hearts. Methylated DNA from cardiac biopsies denoted altered DNA methylation in patients with end-stage cardiomyopathy (Greco & Condorelli, 2015). Failing cardiomyocytes seem to present a methylation profile partially

resembling fetal cells. These observations favor a role for DNA methylation in derangement of gene expression associated with heart failure, although it is premature to tell if such epigenetic change represents the cause or the consequence of heart failure. Additional evidence has suggested a potential mechanism of action for DNA methylation in heart anomalies. Tumor necrosis factor (TNF)-α, a pro-inflammatory cytokine involved in heart diseases and obesity, was shown to directly enhance cardiac methylation through upregulating DNMT1. Angiotensin II, the levels of which are also elevated in cardiometabolic diseases, was also found to promote DNA hypermethylation (Kao et al., 2014). In addition, a number of cardiac insults such as oxidative stress, hypoxia, aging, and toxins, may all produce DNA methylation changes (Greco & Condorelli, 2015; Kao et al., 2014). A number of DNA methylation inhibitors including 5-aza-2-deoxycytidine demethylating agent, polyphenols from fruits, vegetables, dietary components, and cocoa as well as folic acid may confer cardiac protection under various pathological settings possibly through reexpression of hypermethylated silenced genes and alteration in stress environment in the heart (Greco & Condorelli, 2015; Turdi et al., 2013; Voelter-Mahlknecht, 2016). Further study is warranted to elucidate the role for DNA methylation in cardiac pathology and the diagnostic value of circulating blood methylation markers for such in the settings of obesity and chronic metabolic diseases.

DNA methylation regulation in obesity and complications may also be mediated through the cholesterol network. Alterations in 11 BMI-associated cholesterol metabolism genes including genes related to sterol synthesis (CYP51A1, SCD, FADS1, FDFT1, HMGCS1, SC4MOL SQLE), uptake (LDLR, MYLIP), and efflux (ABCA1, ABCG1) are noted to promote increases in cholesterol in obesity. Seven of these genes contain C-phosphorus-G dinucleotides (e.g., ABCG1/cg06500161), which share Encyclopedia of DNA Elements (ENCODE)-annotated regulatory regions with methylation profile regulating levels of BMI and inflammation. Thus, DNA methylation-related changes in cholesterol metabolic genes may serve as a molecular link between obesity/inflammation and certain type 2 diabetic phenotypes (Ding et al., 2015). Besides cholesterol metabolism genes, DNA methylation of adipokines including leptin and adiponectin in adipose tissues and blood are tied to adiposity and body mass. A positive correlation has been identified between DNA methylation of adiponectin gene in adipose tissues and BMI/waist girth or LDL-C levels. On the other hand, DNA methylation of leptin in the blood and adipose tissues is found to be negatively and positively, associated with BMI and LDL-C levels, respectively (Houde et al., 2015). These findings favor a role for leptin and adiponectin epigenetic profiles in adiposity and LDL-C levels. Both leptin and adiponectin are known to directly participate in the pathogenesis of obesity-induced cardiomyopathy (Dong & Ren, 2014; Ghantous et al., 2015; Guo et al., 2013), although further evidence is needed to validate the role of DNA methylation of these two adipokines in the onset and development of obesity cardiomyopathy and the role of LDL-C, if any.

Temple syndrome (also referred to as "maternal UPD 14 phenotype") is characterized by intra-uterine growth retardation (IUGR) accompanied by low birth weight, hypotonia and poor feeding in neonatal life. The patients are usually developmentally delayed particularly in speech in childhood followed by premature puberty, short stature and truncal obesity in adolescence. These patients display a much higher risk of early-onset obesity, type 2 diabetes and cardiovascular diseases. Among various potential factors speculated for the etiology of Temple syndrome, reduced methylation at IG-DMR/MEG3-DMR at the chromosome 14q32 imprinted locus is believed to play a major role in its pathogenesis (Briggs et al., 2016). To this end, understanding of the role of DNA methylation profile may be used to predict prevalence of the disease and provide direction for drugs or diet-related therapy to counter epigenetic changes in patients with Temple syndrome and other forms of obesity cardiovascular complications. For example, DNA methylation profile may be considered as a biomarker for diet-associated weight loss programs (Cordero et al., 2015) and assessment of age-associated risk of metabolic syndrome (Ali et al., 2015). Advanced aging and elevated HbA1c levels are common independent risk factors for non-communicable diseases and may affect blood epigenetic markers of DNA methylation. Methylation levels in the blood and adipose tissues associated with BMI are overrepresented among genes related to pathological conditions such as type 2 diabetes mellitus, cancer, aging and cardiovascular diseases (Ronn et al., 2015).

4. Role of histone modification in obesogenesis and cardiomyopathy

Eukaryotic DNA is packaged into a chromatin structure consisting of histones wrapping DNA. Five histones have been identified in humans: H1, H2A, H2B, H3 and H4. Stable genome may be altered by covalent post-translational modification of histones in response to changes in the environment, resulting in variations in gene expression in pathological states such as metabolic stress. Along with CpG island methylation, histone modifications control the accessibility of nucleosomes for transcription. Histone modifications also influence the binding capacity of other proteins to histones through changes in local hydrophobicity, RNA polymerase status and the binding affinity to other transcription coactivators. Various post-translational modifications at the N-terminals of histones are present including phosphorylation, acetylation, methylation, and ADP-ribosylation. It is rather challenging to decode specific post-translational modifications for individual histones or nucleosomes (e.g., location of nucleosomes in reference to the gene transcriptional start point), although histone modifications are capable of communicating among each another. Factors including sites, types, and degrees of histone modifications all contribute to the complexity of histone code.

Histone acetylation and deacetylation, mediated through coactivator complexes containing histone acetyltransferase (HAT) and co-repressor complexes containing histone deacetylase (HDAC), respectively, represent the primary machineries to control of gene expression. Eleven members of HDAC have been identified, categorized into four classes (I-IV). Histone acetylation via HATs disengages intra- and inter-nucleosomal interactions to loosen up chromatin structure and turn on gene transcription. Histone changes through acetylation (attaching an acetyl group to lysine residues to neutralize its basic charge) or deacetylation using HDACs modulate the euchromatin (accessible) or heterochromatin (inaccessible) state of chromatin (Pasquier et al., 2015). A number of specific HATs and HDACs have been developed to govern cardiovascular homeostasis. In general, the role of HDACs in cardiac hypertrophy and failure has been complex, with some displaying antihypertrophic properties whereas others exhibit pro-hypertrophic features. For example, loss of function of HDAC5 or HDAC9 (two class II HDACs) has been associated with higher susceptibility to cardiac hypertrophy and failure, largely due to their ability to bind and silence MEF2C. In contrast, HDAC4, another class II member, may repress cardiac hypertrophy through inhibiting MEF2 and serum response factor (Greco & Condorelli, 2015).

Direct evidence for histone modification in the pathogenesis of obesity and its organ complications is presently scarce. Recent findings suggest a role for HDACs in cardiometabolic diseases and HDAC inhibitors have been tested in a variety of chronic diseases (Arguelles et al., 2016; Zhang & Ren, 2014). Valproic acid, classified as a nonspecific HDAC inhibitor, along with trichostatin A and butyric acid, are commonly used in the management of mood disorders and epilepsy to promote visceral obesity in humans by increasing newly formed adipocytes, similar to corticosteroids. It has been shown that glucocorticoid receptor stimulates adipogenesis in part by enhancing the transcription of C/ebpa through the titration, and subsequent degradation, of HDAC1 from the C/ebpα promoter (Kuzmochka et al., 2014). Therefore, targeting HDAC1 (likely through activation) may serve as a possible avenue to prevent glucocorticoid-induced adiposity through regulation of CCAAT/enhancer-binding protein α (C/EBPα) levels in preadipocytes.

Along the same line, inhibition of HDAC3 activates PPARγ to improve insulin sensitivity in diet-induced obesity (Jiang et al., 2014).

PPARγ activation by exogenous ligands including thiazolidinediones is commonly used in the therapeutics of type 2 diabetes mellitus to enhance insulin sensitivity. HDAC3 is capable of interacting with PPARγ to deacetylate the protein, thus inducing PPARγ function in the absence of a ligand. This is supported by enhanced expression of PPARγ target genes such as adiponectin and aP2, leading to an increase in glucose uptake and insulin signaling in adipocytes, as well as enhanced lipid accumulation during differentiation of adipocytes, following HDAC3 inhibition. Thus, in the absence of thiazolidinediones, acetylation from HDAC3 inhibition may induce the transcriptional activity of PPARγ (Jiang et al., 2014).

HDAC3 plays an essential role in cardiac progenitor cell differentiation to regulate cardiogenesis. Mouse embryos lacking HDAC3 in cardiac progenitor cells display developmental defects in the heart, elevated Tbx5 target genes and embryonic lethality. Here HDAC3 is believed to interact with Tbx5 to directly modify its acetylation state, leading to the repression of Tbx5-dependent cardiomyocyte lineage-specific genes (Lewandowski et al., 2014). Histone modification is also demonstrated to mediate a number of pharmacotherapy effects in obesity. In mouse adipose tissues from diet-induced obesity, the binding of HDACs 1, 2 and 6 is elevated at the leptin promoter. It is believed that histone modifications serve a feedback mechanism to keep leptin levels somewhat constant within a normal range. In addition, n − 3 polyunsaturated fatty acids (n − 3 PUFAs) may counter adiposity via epigenetic regulation of leptin including histone modifications (Shen et al., 2014). Moreover, mitogen-activated protein kinase phosphatase 3 (MKP-3) may exert a pivotal role in obesity-induced hyperglycemia through facilitating hepatic glucose output. A global phosphoproteomic analysis of the MKP-3 downstream mediators has identified a unique role for HDAC in MKP-3-induced hepatic lipid metabolism. MKP-3 inhibition is capable of facilitating energy expenditure, peripheral glucose disposal, and insulin signaling in association with phosphorylation of HDAC 1 on serine 393 and HDAC2 on serine 394. HDAC1/2 is increased in livers of MKP-3 knockout mice fed a high fat diet to mediate the MKP-3 inhibition-offered metabolic benefits (Feng et al., 2014). These observations are in line with the downregulated transcript levels of HDAC2 and cardiac α-actin in murine hearts following a two-week Western diet feeding. Further study revealed that repressor element 1-silencing transcription factor REST orchestrates the level of chromatin in diet-induced hypertrophy (Medford et al., 2014). Deacetylation and dephosphorylation of histone H3 has also been reported in the hearts of diabetic Sprague–Dawley rats, responsible for changes in gene expression in the extracellular matrix (ECM) and cardiac hypertrophy (Gaikwad et al., 2010). Global histone methylation is relatively unclear in obesity, although substantially decreased levels of histone H3 lysine 4 dimethylation has been reported in adipocytes from overweight individuals while increased levels of lysine 4 trimethylation were noted in obese/diabetic patients (van Dijk et al., 2015).

5. Role of non-coding ribonucleic acid in obesogenesis and cardiomyopathy

Next-generation sequencing has enriched our understanding of the mammalian transcriptome, revealing a pivotal role for non-coding RNAs (ncRNAs), transcripts encoded by the genome and transcribed but never translated, in both physiological and pathophysiological conditions. Two classes of ncRNA namely microRNA (miRNA) and lncRNA (long non-coding RNA) are identified with essential roles in gene regulation of cardiometabolic functions (Xu et al., 2015). Following the recent advances in the human genome from the ENCODE and FANTOM consortia, the term “genomic noise” related to ncRNAs has drawn some intense attention. Dysregulation of ncRNAs are associated with the onset and progression of cardiovascular and metabolic diseases, suggesting the therapeutic potential of targeting ncRNAs in cardiovascular and metabolic diseases (Arner & Kulyte, 2015; Marques-Rocha et al., 2015). Both microRNAs and lncRNA are capable of regulating gene expression in diseases. Several miRNAs are involved in the control of metabolism and energy homeostasis (Dumortier et al., 2013; Rizki & Boyer, 2015) with a tissue-specific impact on insulin sensitivity.

miR-103/107 stabilizes insulin receptors in the liver and adipose tissues by targeting caveolin-1 (Trajkovski et al., 2011). The miR-29 family has been revealed to govern the balance between homeostatic and disturbed glucose handling in diabetes and obesity. In particular, both miR-29a and miR-29c serve as negative regulators of insulin signaling via phosphatidylinositol 3-kinase (PI-3K) regulation. Global or hepatic insufficiency of miR-29 retards obesity and diet-induced insulin resistance (Dooley et al., 2016). Moreover, miRNAs are directly linked to inflammation and adiposity. Cardiac-specific miR-208a inhibition displays resistance to obesity, improved glucose and lipid profiles in mice, a systemic energy regulatory effect through MED13 (Grueter et al., 2012). Along the same line, inhibition of the let-7 family members and miR-143 offers protection against insulin resistance-associated obesity by targeting the insulin receptor, insulin receptor substrate 2 (IRS2) or oxysterol-binding-protein-related protein (ORP) 8 (Frost & Olson, 2011; Jordan et al., 2011). More recent evidence suggested a novel regulatory role for miR-192-3p in adipocyte differentiation and lipid homeostasis using stearoyl coenzyme A desaturase-1 and the fatty aldehyde dehydrogenase ALDH3A2 (aldehyde dehydrogenase 3 family member A2) as direct targets of miR-192-3p (Mysore et al., 2015). On the other hand, miR-802 may disturb glucose metabolism through silencing of hepatic Hnf1b (Kornfeld et al., 2013).

With regards to the heart, high fat diet feeding is suggested to trigger atrial arrhythmia (manifested as prolonged P wave, increased inducibility of sustained atrial tachycardia and reduced atrial conduction velocity) via down-regulation of Cx40 in a miR-27b-dependent manner, a process deemed independent of inflammation (Takahashi et al., 2016). High fat diet intake also alters the miRNA signature in cardiac remodeling. In recent work from Guedes and colleagues, Western diet (45% fat) intake for 10 and 20 weeks altered the levels of 64 and 26 miRNAs in the heart, respectively. On the other hand, 60% high fat diet intake for 10 and 20 weeks perturbed the homeostasis of 27 and 88 miRNAs in the heart, respectively. Further bioinformatics analysis revealed overrepresented insulin signaling pathway in response to fat diet intake. Also, cardiac levels of Glut4 were found to be inversely correlated with miRNA-29c. Inverse correlation between GSK3β and the levels of miRNA-21a-3p, miRNA-29c-3p, miRNA-144-3p and miRNA-195a-3p was also noted (Guedes et al., 2015). The presence of obesity in heart failure patients is linked to a differential expression of selected miRNAs, some of which (e.g., miR-221/-130b) directly regulate adiposity (Thome et al., 2015). Many miRNA families have been reported to regulate insulin sensitivity and adiposity including let-7, miR-17/92, miR-29, miR-103/107, miR-130, miR-143-145, miR-192, miR-200, miR-221/222, miR-223, and miR-375 (Deiuliis, 2016). Additionally, several miRNAs such as let-7, miR-125, miR-126, miR-132, miR-146, miR-155 and miR-221, have emerged as key transcriptional regulators for inflammation underpinning obesity (Marques-Rocha et al., 2015). These findings suggest the promises of miRNA-based therapeutics as an innovative treatment modality for obesity and inflammation. In addition, miRNA levels in plasma or body fluids may be considered as biomarkers for obesity and other metabolic diseases (Deiuliis, 2016).

Unfortunately, the complexity of lncRNAs makes it somewhat difficult to characterize their roles in cardiometabolic pathologies. Recent evidence suggests a key role for lncRNA in the maintenance of genomic integrity, genomic imprinting, control of protein-coding genes and mRNA processing. Disturbance in lncRNAs may promote a wide array of chronic diseases, including cardiometabolic diseases, cancer, immune and neurological disorders (Bhan & Mandal, 2014). More recent evidence suggested that lncRNAs may be associated with distant transcriptional enhancers (the so-called super-enhancers) and play fundamental roles for enhancer activity and the regulation of genetic programs (Ounzain & Pedrazzini, 2015). A detailed characterization of the mechanism behind these ncRNAs should be conducive to a better

understanding of the cellular processes underlying metabolic disease such as obesity and type 2 diabetes, in an effort to develop innovative therapeutic strategies (Elia & Condorelli, 2015).

ncRNAs regulate transcriptional and posttranscriptional gene expression and translation of mRNAs to proteins, contributing to the pathogenesis of obesity and heart diseases. Various miRNAs participate in the regulation of adiposity, metabolism and heart homeostasis-related pathways, such as glucose uptake, insulin signaling, insulin secretion, cholesterol and lipid homeostasis, adipogenesis, cell and tissue stress, cardiac contractile function, cardiac modeling, and inflammatory responses (Rottiers & Naar, 2012). Nonetheless, it is unclear at this stage the precise role of ncRNAs in obesogenesis. Given that ncRNAs and their targets are encoded in the genome despite not being translated, genetic rules apply, thus resulting in variations in the functionality of ncRNAs and subsequent differential regulation of their target genes (Calore et al., 2015). For example, a comprehensive analysis of genomic variations in the lncRNA loci reveals a distinct distribution of variations in subclasses of lncRNAs and potential functional domains of lncRNAs (Bhartiya et al., 2014). It may be expected that genetic variations or polymorphisms in ncRNA or their target genes also contribute to the onset and development of adverse phenotypes of cardiometabolic diseases (Calore et al., 2015).

6. Transgenerational impact of nutrition on fetal and adult health later in life

Inheritance is determined in the DNA sequence, an established gold standard principle of modern genetics. However, DNA sequence is not the sole decisive factor responsible for passing information between generations, thereby producing phenotypic diversity. The epigenome is deemed an interface between genome and environment for not only manifestation of phenotypes but also stability of phenotypes throughout one's life course. Parental behavior, diet and fitness may influence the phenotype of offspring generation through epigenetic transmission, favoring a unique role for environment on health and disease susceptibility independent of the genetic susceptibility (Reddy & Natarajan, 2015). It is perceived that ecologic factors, parental genetics, fitness and diet, as well as intrauterine environment, may drastically impact the prevalence of metabolic anomalies and other unfavorable health consequences in later generations (Lane, 2014).

Numerous epidemiological studies have identified a pivotal role for fitness, diet, stress, tobacco and alcohol, diabetes, and hypertension during gestation in fetal development. Not surprisingly, epigenetic factors such as DNA methylation and chromatin modifications during gestation may contribute to diverse plasticity including oral clefts, congenital heart defects, neural tube defects, autism spectrum disorder, allergies and cancer (Barua & Junaid, 2015). Along the same line, environmental factors experienced during early stages of development, including the intrauterine and neonatal periods, are believed to predispose individuals to the elevated prevalence of metabolic diseases such as obesity, insulin resistance and type 2 diabetes (Jimenez-Chillaron et al., 2016).

Although transgenerational epigenetic inheritance has been well documented in plants and fungi, it has not been confirmed in mammals until recently. Early life nutrition and maternal diet have been demonstrated to influence the risk of metabolic disorders including obesity, insulin resistance, type 2 diabetes and cardiovascular diseases, later on in life. Environmental components are known to produce overt changes in the genome activity without altering the DNA sequence, possibly resulting in epigenetic memory and transgenerational changes in health phenotype. Moreover, epidemiological evidence has revealed an increased risk of hypertension and cardiovascular diseases in offspring of women with preeclampsia. Multivariate analysis suggests maternal central pulsatile blood pressure components (SBP and PP) during pregnancy are associated with higher blood pressures in the offspring (Lim et al., 2015). However, the epigenetic cue triggering such changes in SBP and PP has not been identified. To better dissect the role of intrauterine and neonatal environmental factors in the onset and progression of disease later on in life, it is pertinent to understand the physiological and/or pathophysiological impacts of specific nutrients on human epigenome and how dietary interventions during intrauterine and neonatal life may affect disease prevalence through epigenomic modifications (Lee, 2015).

As a good example of transgenerational inheritance, epigenetic modification in the agouti viable allele (Avy) may produce changes in fur color and an obesity/diabetes-like phenotype, an aberrant phenotype passed on to later generations via epigenetic regulation in the female germline. Mammalian germline reprogramming refers to the erasure and re-establishment of epigenetic information essential to germ cell function and inheritance in offspring (Hogg & Western, 2015). Epigenetic inheritance is also present in humans although at a much lesser extend compared to rodents. Concomitant germline mutation and epimutation in the human DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2 are believed to be associated with Lynch syndrome, an inherited predisposition cancer syndrome that may be transmitted to the offspring (Cini et al., 2015). Heritable risk may be epigenetically transmitted over generations without the presence of a continued exposure to stimuli. Given the fast rising prevalence of obesity and metabolic disorders in the 21st century, a much better understanding of the role for transgenerational inheritance in the pathogenesis of metabolic derangements will help to identify new therapeutic targets for the prevention, diagnosis and treatment of such comorbidities.

There is irrefutable experimental and epidemiological evidence for a role of nutrient and environmental exposures during pregnancy including high-fat or high-sugar diets, low-protein diets, various toxins, and ancestral genetic variants in transgenerational inheritance resulting in offspring obesity and associated metabolic abnormalities (metabolic syndrome). Using organisms encompassing from *Caenorhabditis elegans* to *Mus musculus* to *Sus scrofa*, transgenerational inheritance is speculated to contribute to human metabolic risk (Stegemann & Buchner, 2015). Although the basis behind transgenerational inheritance of metabolic diseases still remains elusive, the concept of "gestational programming" likely results from alterations in the epigenome (nongenomic small RNAs, histone modification, and DNA methylation) rather than in the DNA sequence (genomic) (Desai et al., 2015). In general, the thrifty phenotype hypothesis, epigenetic mechanisms and development plasticity are deemed as fundamental factors involved in health and disease throughout life. To this end, it may be speculated that cardiometabolic events and obesity originate from intrauterine nutritional deficiency, associated with a food supply that is excessive to the metabolic needs of the organism in early life stages, which promotes catch-up growth in an effort to recover from intrauterine constraint. Depending on nutritional adequacy in the first years of life, developmental plasticity may lead to phenotype reprogramming and reduce the risk of obesity (Ribeiro et al., 2015). Malnutrition during gestation may cause intrauterine growth retardation and low birth weight, which may result in postnatal catch-up growth and consequently onset and development of obesity and type 2 diabetes. In addition, obesity and type 2 diabetes may also be programmed transgenerationally through maternal substance abuse (e.g., psychoactive substances including illicit drugs or alcohol) during gestation and lactation (Stegemann & Buchner, 2015).

A growing body of evidence also indicates a key role for fathers in transgenerational inheritance. Changes in paternal diet result in transgenerational inheritance of the insulin-resistant phenotype, consolidating diet-induced epigenetic reprogramming via paternal lineage (Soubry, 2015). Using an established *Drosophila* model of diet-induced intergenerational metabolic reprogramming, it was revealed that as little as 2 days of dietary intervention in fathers may trigger obesity in offspring. Epigenetic machineries including DNA methylation, histone modification, and ncRNAs are believed to be responsible for such epimutations. In particular, paternal sugar serves as a suppressor of variegation, desilencing chromatin-state-determined domains in male germline and offspring embryos. H3K9/K27me3-dependent

reprogramming of certain metabolic genes were identified in two critical germline and zygotic windows (Ost et al., 2014). Paternally-induced transgenerational inheritance for obesity and metabolic disorders has also been confirmed in mammals. Changes in paternal diet and fitness have been shown to initiate environmental reprogramming and promote obesity susceptibility and phenotype variation in mice and humans (Carone et al., 2010; Murashov et al., 2016; Soubry, 2015), providing more insights into the mechanisms behind intergenerational reprogramming and phenotypic variations for obesity and metabolic disorders.

7. Genome-wide analysis and obesity

Complex anthropometric traits are often the consequence of interactions among various genetic and environmental factors without following the Mendelian rule of inheritance. It is perceived that anywhere from several to hundreds of genes with individually less predominant effects contribute to such non-Mendelian inheritance phenotypes. In particular, the obesity trait may be induced by epigenetic influences including dietary fat intake and environmental cues. These epigenetic patterns are likely established during early life to predispose or program obesity and its comorbidities later on in adult life. Identification of novel obesity-associated polymorphisms may be achieved by Genome-Wide Association studies (GWAS). Findings from GWAS have identified many variants of small effect for complex traits in a given physiological or disease setting, in line with the non-Mendelian inheritance pattern. However, a confounding issue is that the allelic polymorphisms or DNA mutations identified by GWAS can only explain a small fraction of the expected heritability of physiological or pathological traits. Several explanations have been suggested for this phenomenon known as “missing heritability,” including unidentified rare variants of large effect, epistatic interactions, and overinflated heritability estimates (Dick et al., 2014).

In light of the fact that DNA sequence is not the sole determinant for information relay between generations to control phenotypic diversity, a new paradigm in epigenetic modifications (DNA methylation and chromatin assembly) has gained attention for the high plasticity of the genome and inherited vulnerability to disease across generations. It is confirmed that epigenetic programs may account for a significant fraction of the “missing heritability” (Trerotola et al., 2015). Somewhat distinct from the stable DNA inheritance, epigenetic program incorporates the information of acquired disease traits to allow inheritance of an epigenetic phenotype to offspring who are never exposed to the original stimuli. This notion of epigenetic inheritance has profound implications for disease etiology from the perspective of evolution (Dick et al., 2014).

Using the HumanMethylation450 BeadChip, genome-wide DNA methylation pattern was examined in the liver to reveal 251 individual methylated CpG sites with differential DNA methylation in type 2 diabetic patients compared with non-diabetic subjects. Some of the CpG sites are annotated to genes relevant to the risk of type 2 diabetes, including GRB10, ABCC3, MOGAT1 and PRDM16. In addition, a large majority of CpG sites (94%) exhibited reduced DNA methylation in livers from diabetic subjects. It is believed that reduced folate levels may be attributed to the hepatic hypomethylation in diabetes, consistent with the findings of low erythrocyte folate levels in these patients (Nilsson et al., 2015). This finding supports a role for epigenetic modifications due to nutrient factors in the liver from type 2 diabetic subjects. In another independent epigenome-wide analysis, eight CpG sites were found to be associated with BMI while five CpG sites were tied to waist circumference, replicating the top hits in the Framingham Heart Study and the Atherosclerosis Risk in Communities study. Among these blood epigenetic markers, CPT1A, PHGDH and CD38 were among the top hits associated with both BMI and waist circumference. The ncRNA 00263 was found to correlate with BMI and waist circumference (Aslibekyan et al., 2015). This sort of large-scale EGWAS study is able to identify robust and replicable associations between DNA methylation at CpG loci and common obesity traits, which should offer guidance for future development of diagnostics and therapeutics in obesity.

GWAS is also used to identify disease-relevant genomic regions. To understand the basis of the association between obesity and the FTO gene, which displays the strongest genetic tie to obesity (Ehrlich & Friedenberg, 2016), epigenomic profile, allelic property, motif conservation, regulator expression and gene coexpression patterns were examined using endogenous CRISPR-Cas9 technique. The FTO allele associated with obesity is found to repress mitochondrial thermogenesis in adipocyte precursor cells. The rs1421085 single nucleotide mutation (T-to-C) impairs a conserved motif for the ARID5B repressor, resulting in the relief of a preadipocyte enhancer and an increase in IRX3/IRX5 level during early adipocyte differentiation. Consequently, a cell-autonomous change develops shifting the energy-dissipating beige adipocytes to become energy-storing white adipocytes, leading to an 80% drop in mitochondrial thermogenesis and a dramatic increase in lipid storage (Claussnitzer et al., 2015).

DNA elements exist downstream from the BMI-associated FTO locus, regulating the expression of IRX3 and IRX5. Long range interaction has been demonstrated between the regulatory elements in the FTO locus and the IRXB cluster genes IRX3/IRX5, governing adiposity and thermogenesis (Rask-Andersen et al., 2015). This is supported by the notion that inhibition of IRX3 in adipose tissues promotes energy dissipation and lowers body weight without affecting physical activity or appetite. Likewise, knockdown of IRX3 or IRX5 in primary adipocytes from individuals with the risk allele restores thermogenesis, while elevation of these genes confers detrimental effects in adipocytes from nonrisk-allele carriers. CRISPR-Cas9 editing correction of rs1421085 repairs the ARID5B motif and may restore IRX3/IRX5 repression, activate adipocyte browning, and promote thermogenesis in primary adipocytes from patients with the risk allele (Claussnitzer et al., 2015). These data depicted the pro- and anti-obesity roles for ARID5B, rs1421085, and IRX3/IRX5 in adipocyte browning and thermogenesis.

Genome-wide leukocyte DNA methylation variation was examined in 30 healthy young adult monozygotic twins with disparate BMI. Stratification of the twin pairs according to liver fat accumulation revealed two epigenetically distinct groups. DNA methylation differences were present if the heavier co-twins displayed excessive liver fat, an unhealthy obesity pattern coupled with insulin resistance and inflammation. Twenty three genes associated with liver fat, type 2 diabetes mellitus, obesity and metabolic syndrome were differentially methylated with CpG sites overrepresented at promoters, insulators, and heterochromatic and repressed regions. Repressed and weakly transcribed sites were significantly more likely to be hypomethylated, whereas sites with strong enhancers and active promoters were likely to be hypermethylated (Ollikainen et al., 2015). The altered methylome in leukocytes may indicate several novel candidate genes and pathways in obesity and obesity-related complications.

8. Impact of food intake, energy expenditure and adiposity on epigenetics

Given that epigenetic modifications are mainly controlled by lifestyle and diets, dietary phytochemicals have gained recognition as promising and effective sources for intervention with these epigenetic processes and molecular targets and are known to stimulate obesogenesis. The rapid advance in the analysis of the metabolome has paved the way to understand the complex progression of obesity and treatment outcome (Paul et al., 2015). Among many dietary factors, folate and synthetic folic acid may serve as donors for the one-carbon units to regulate programming of epigenetic processes during early development (Kok et al., 2015). Folate and other vitamin deficiencies during embryonic development constitute an independent risk factor for neural tube defects and cardiovascular and metabolic disorders (Wang et al., 2012).

Despite a recognized role for epigenetics in fetal programming, dietary supplementation with functional amino acids, vitamins, and phytochemicals in the prevention and management of metabolic syndrome is still in its infancy. In a randomized, placebo-controlled trial on effects of folic acid and vitamin B12 on bone fracture [B-vitamins for the PRevention Of Osteoporotic Fractures (B-PROOF) study], 162 (versus 14 in placebo group) of the 431,312 positions were found to be differentially methylated following intervention with folic acid and vitamin B12, suggesting the potential utility of long-term supplementation with folic acid and vitamin B12 in the elderly through DNA methylation of genes (Kok et al., 2015). Another dietary factor curcumin (diferuloylmethane), a polyphenolic compound commonly known as turmeric, may also modulate many disease processes including cardiovascular diseases, neurocognitive disorders, cancer, inflammation, and obesity via epigenetic regulation. Inhibition of DNMTs and regulation of histone modifications (through HAT and HDAC) and ncRNA are perceived the main epigenetic regulatory machineries for curcumin (Boyanapalli & Tony Kong, 2015). Moreover, dietary components such as epigallocatechin-3-gallate (EGCG) in green tea and sulforaphane in cruciferous vegetables may also regulate epigenetic processes including DNMT inhibition, histone modifications (through HDAC and HAT), and ncRNA regulation. An epigenetic diet was shown to affect longevity and carcinogenesis via modulation of certain genes encoding telomerase and p16 (Daniel & Tollefsbol, 2015). Amino acids (e.g., glycine, histidine, methionine and serine) and vitamins (B6, B12 and folate) are currently the main dietary supplements in provision of methyl donors for DNA and protein methylation (Ji et al., 2016). It is noteworthy that epigenetic modulation occurs in response to dietary factors, which may affect or be affected by gut microbiota. Gut microbiome interacts with dietary factors to influence certain epigenetic processes and human health. Last but not least, caloric restriction may impose a pivotal role in advanced aging and metabolic diseases. Caloric restriction may alter epigenetic modulation and prolong life-span in various experimental models. Likewise, limiting glucose consumption may also lower the risk of aging-associated chronic diseases such as diabetes and cancer (Daniel & Tollefsbol, 2015).

Besides dietary factors regulating epigenetic modulation of metabolic traits, neuronal control of appetite and energy expenditure from hypothalamic circuits located in the arcuate nucleus may be disturbed by maternal nutritional challenge during early life. More evidence has identified epigenetic regulation of hypothalamic genes as possible mechanisms linking maternal diet during gestation to the prevalence of obesity and metabolic derangement later on in life. Perturbed nutrition in pregnancy including maternal under- and over-nutrition may predispose offspring to metabolic defect, supporting the developmental origins of obesity and metabolic syndrome (Gali Ramamoorthy et al., 2015). Along this line, gestational exposure to maternal hyperglycemia increases the risk of obesity later on in adult life. It is believed that epigenetic mechanisms involving leptin surge during the perinatal period in response to maternal hyperglycemia plays a pivotal role for fetal programming of adult onset metabolic disorders including obesity. DNA methylation near the leptin gene locus seems to control the correlation between maternal glycemic levels and neonatal leptin with high cord blood levels of leptin associated with lower DNA methylation at cg12083122 (Allard et al., 2015).

9. Epigenetics and other organ (non-cardiac) complications in obesity

There is tantalizing evidence that modifications to DNA and histones may be one avenue through which obesity confers susceptibility to the development of obesity complications in many other organs. The growing epidemic of obesity, along with increased aging populations, has led to a significant rise in the prevalence of obesity complications related to liver, kidney diseases, sleep dyspnea and cancer (Bhaskaran et al., 2014). Obesity is a major risk factor for colorectal cancer. Profile of histone modifications to predict enhancer use in the colon in diet-induced and genetic obesity revealed close resemblance to colorectal cancer for the enhancer profile. Chronic inflammation associated with obesity is one potential mediator although high serum lipid levels associated with inflammation may also play a role (Schones et al., 2015). Another example is the similarity between vitamin B12 deficiency and multiple sclerosis in pathological traits, including conduction disturbances. One possible mechanism may be related to vitamin B12-dependent methionine metabolism, which is defective in multiple sclerotic brains. Levels of the methyl donor betaine are low in multiple sclerosis and are correlated with reduced histone H3 methyl mark H3K4me3 in cortical neurons. Methionine metabolism plays a role in neurodegeneration in multiple sclerosis, possibly associated with regulation of mitochondrial respiration, including electron transport chain gene expression and energetics. A reduction in the methyl donor betaine is correlated with reduced histone H3 trimethylation (H3K4me3) in NeuN+ neuronal nuclei in multiple sclerosis. Chromatin immunoprecipitation findings showed that betaine regulates metabolic genes in SH-SY5Y neuroblastoma cells. These data suggest that altered methionine metabolism may be tied to changes in neuronal energetics in multiple sclerosis cortex (Singhal et al., 2015).

Parental behavior, fitness and diet influence the physiological and disease phenotypes of later generations through epigenetic transmission, favoring a unique role for environment in disease susceptibility. On the other hand, characterization of how the epigenome may be affected by metabolic disharmony should offer novel insights for the onset and progression of metabolic diseases. Individuals with obesity are deemed to be at increased risk of developing pre-mature aging-related chronic diseases such as cancer, inflammation, type 2 diabetes and heart diseases (Sargent, 2015), although the molecular underpinnings remain elusive for these pre-mature aging pathologies in the context of obesity. Recent evidence has suggested that the acceleration of the 'epigenetic clock' in obese liver may serve as a molecular link between obesity and pre-mature aging anomalies (Horvath et al., 2014).

10. Pharmacological intervention of epigenetics in human obesity

The field of epigenetics has experienced a remarkable expansion in the past few years with advances in biology, epigenomic technologies and drug development. Yet it is still challenging to develop novel and effective pharmacotherapy for obesity and cardiovascular diseases targeting epigenetics with the limited knowledge of how the cell epigenome is regulated by metabolic stimuli (Reddy & Natarajan, 2015). Pharmacological therapy targeting DNA methylation has proven beneficial for cardiac and metabolic pathologies. Epigenetic therapies inhibiting DNMTs or HDACs have offered some clinical promises. To date, three HDAC inhibitors, Zolinza (Vorinostat), Istodax (Romidepsin), and Beleodaq (Belinostat), as well as two DNMT inhibitors, Vidaza (5-Azacytidine) and Dacogen (Decitabine), have been approved by the FDA to treat certain cancers such as lymphoma, leukemia and myelodysplastic syndromes (Hamm & Costa, 2015). A few more HDAC and DNMT inhibitors are now in the investigative stage or pre-clinical trials.

Other promising candidates targeting ncRNAs such as miRNAs and lncRNAs have also shown some promise as important modifiers of the epigenome. With regards to what, when and how treatment should be provided using the epigenetic concept, no clear guideline is available at this time. Despite the proven merit for sodium restriction and nutrient supplement to suppress DNA methylation, whether other more potent or stringent measures should be considered for the control of lipid and glucose levels in obese individuals is still an issue of much debate. Some concerns have surfaced as most of these drug candidates are unspecific and, therefore, may create a large-scale epigenetic deregulation. Thus, it is pertinent to develop more specific and effective therapies targeting only particular epigenomic elements. Timing of intervention is also an issue. Should earlier intervention and more aggressive targets

be used at a later point? Despite all these controversies, pharmacological therapy targeting the epigenome is expected to offer great utilities in clinical practice. This is helpful to reverse the early life deleterious epigenetic programming, at least in part, using epigenetically-based pharmacotherapy along with psychosocial modification later in life (Labonte et al., 2012). For example, intensive practice of mindfulness meditation may lead to alterations of histones H4ac and H3K4me3, as well as lowered levels of HDAC genes (*HDAC* 2, 3, and 9) and pro-inflammatory genes (*RIPK2* and *COX2*) in comparison with controls (Kaliman et al., 2014).

The ability to reverse or correct disturbed epigenetic patterns through epigenome-based therapy will help to alleviate and prevent a number of chronic diseases (Vaiserman, 2015a). Given that epigenetic modifications may represent important biomarkers, epigenetic profiles should be beneficial for patient stratification, candidate disease pathway identification and selection of targets for epigenetic therapies. It was reported that higher levels of LDL particles (LDL-P) and lower levels of HDL particles (HDL-P) may predict for risk of coronary heart disease among severely obese postmenopausal women (Mackey et al., 2015). Moreover, extra-cardiac fat mass is correlated with BMI while pericoronary fat mass is independently associated with risk of coronary artery diseases. Inflammatory biomarkers display a positive correlation with pericoronary fat, suggesting a role for systemic inflammation in the pathogenesis of coronary artery diseases (Maurovich-Horvat et al., 2015).

It is of important clinical value to identify the "BMI" relevant epigenetic biomarkers for coronary heart diseases. Recent seminal work from Dalgaard and colleagues has identified a Trim28-dependent network in obesogenesis. Trim28 mutant mice displayed a bi-modal body-weight distribution, with an imprinted gene network including Nnat, Peg3, Cdkn1c, and Plagl1 likely being responsible for the on-switch of obesity. Adipose transcriptome analyses confirmed distinct sub-populations in children with stratification based on Trim28 and obesity-associated imprinted gene expression (Dalgaard et al., 2016). This brilliant notion of epigenetic on- and off- switch in obesogenesis for a given genome coding may point to a new direction for pharmacological drug development targeting the potential "on-and-off" switch for obesity phenotype manifestation.

11. Summary

Epigenetic modifications, including DNA methylation, histone modification in chromatin and ncRNA, serve as the interface between a stable genome and the changing environment. Here we summarized the current status of the epigenetics field related to obesity (as briefly depicted in Fig. 3) with a focus on cardiac complications. Given that epigenetic marks are usually reversible and non-permanent, a better understanding of molecular machineries underlying the life course effects of early adverse exposure should help to identify novel and effective therapeutic regimens targeted to the removal of unfavorable epigenetic marks. With the advances in technologies and appearance of affordable high-throughput screen methods, there have been more large scale studies and genome-wide association analyses for the relationships between epigenome and complicated disease states. Epigenetic code has revealed utilities in the diagnosis, prognosis and treatment of obesity and comorbidities (Horsburgh et al., 2015; Neufer et al., 2015). Environmental stimuli, such as diet, exercise and inflammation, may all influence epigenomic processes and must be considered (Neufer et al., 2015). Given complexity of fundamental epigenomic biology, at both cellular and organismal levels, interactive research efforts utilizing more mutually informative model systems should help to confer the best option for breaking ground on new information of epigenetics in obesity and cardiovascular complications.

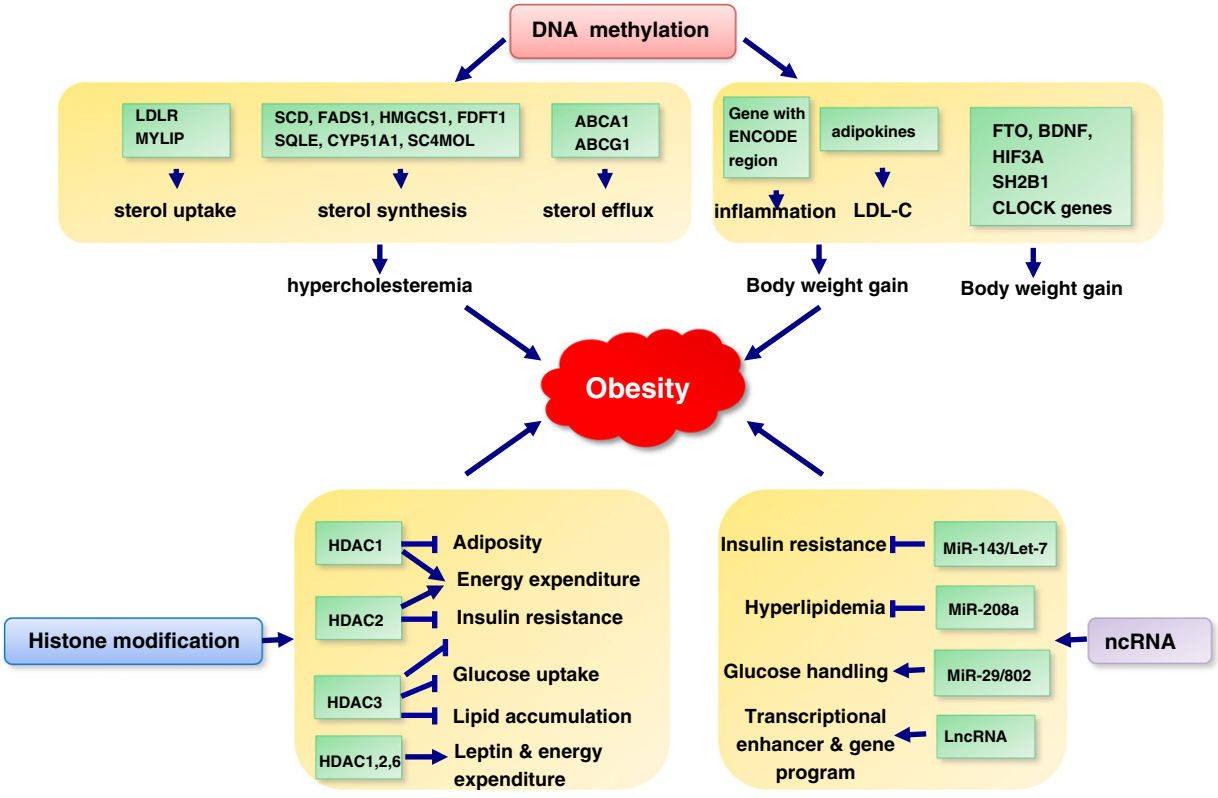

Fig. 3. Examples of certain target genes and non-coding RNAs involved in various epigenetic modifications including DNA methylation, histone modifications and ncRNA transcriptional regulation in obesity pathology.

Conflict of interest

The authors declare that there are no conflict of interest.

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