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Epigenetic crosstalk: a molecular language in human metabolic disorders

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1. ABSTRACT

Technological breakthroughs are emphasizing the impact of epigenetic mechanisms in human health highlighting the importance of a fine-tune orchestration of DNA methylation, micro RNAs, histone modifications, and chromatin structure. Transcriptional regulators sense the concentration of intermediary metabolites associated to a wide variety of biological processes including the long-term imprinting and heritable DNA methylation. Recent epigenetic mechanisms associated with cholesterol and lipid homeostasis have a critical impact in the susceptibility, development and progression of complex diseases such as type 2 diabetes mellitus, non-alcoholic fatty liver, obesity and metabolic syndrome. The heritability of epigenetic states emerge as an additional level of complexity where the extension of somatic as well as inherited epigenetic modifications may require a thoughtful reconsideration in many human diseases related with metabolic disorders.

2. INTRODUCCION

The concept of epigenetics has been in constant debate because of the involvement of multiple mechanisms leading to the epigenetic phenotype (1). In this review we will refer to epigenetics as to heritable changes in gene expression that are not due to changes in the primary DNA sequence, being essential for gene transcription, development, and differentiation of cells and organisms (2). In this context, three major events are mainly involved in the epigenetic regulation: DNA methylation, non-coding RNAs (ncRNAs), and histone post-translational modifications (PTMs). Organisms and individual cells can accurately adapt to environmental changes through the plasticity that is associated to the epigenetic regulation (3). Eventually, the cellular transcriptional machinery and the coordination of transcriptional programs determine cell fate in a given time and specific cellular context. Therefore, the interplay of these regulatory mechanisms establishes the epigenetic state defined as the final configuration of chromatin and DNA marks (4).

Epigenetics is intricately linked to changes in cellular metabolism and these two processes cannot be fully understood separately (5). How gene expression is stably reprogrammed in response to environmental stimulus? How levels of cellular metabolites determine the epigenetic state? How important is the transgenerational epigenetic inheritance in human metabolic disorders? Fundamental key questions about how epigenetic modifications regulate gene expression and activity remain still elusive. In this review, a particular attention to metabolism and transcriptional regulation by the circadian system will be considered focusing on epigenetic modification associated with complex traits such as non-alcoholic fatty liver, obesity and diabetes.

3. THE EPIGENETIC LANGUAGE

Epigenetic mechanisms trigger a set of molecular and biochemical reactions determining the final epigenetic status in which processes such as DNA methylation, microRNA (miRNA) expression, and histone post-translational modifications (PTMs) play a key role in transcriptional regulation and energy homeostasis.

DNA methylation is a covalent chemical modification, resulting in the addition of a methyl

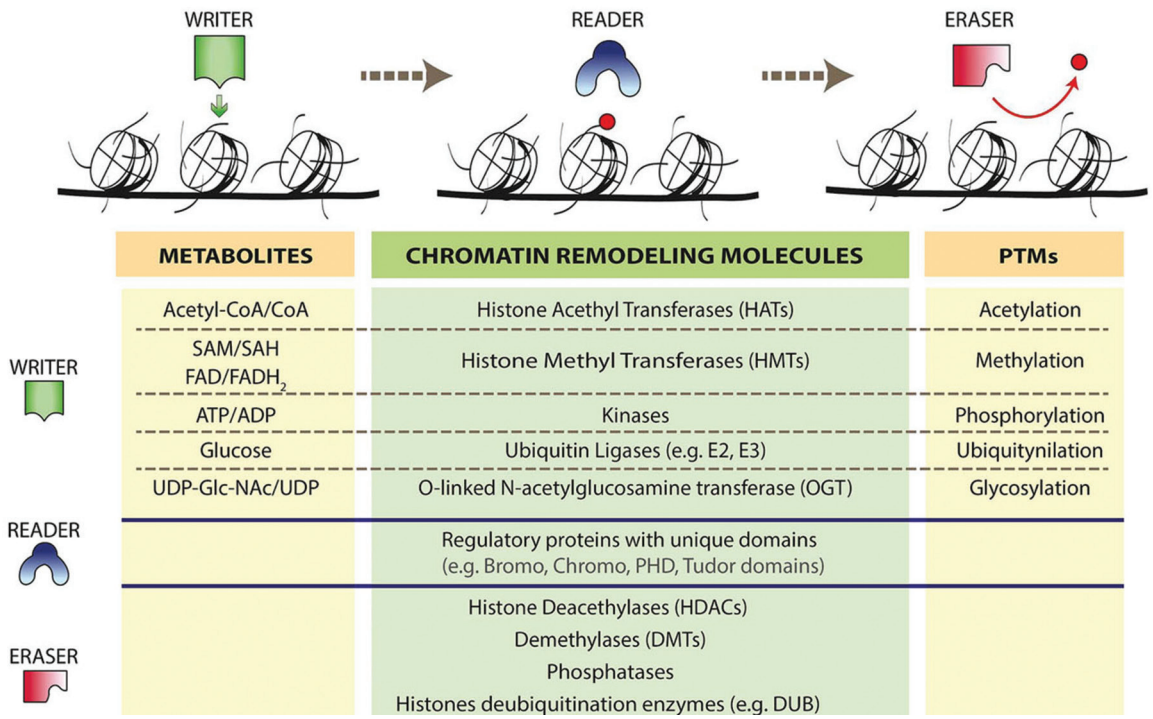

Figure 1. Chromatin remodeling factors determine the chromatin epigenetic state sensing the level of metabolites produced in response to developmental and environmental factors.

group at the 5' position of the cytosine base from S-adenosylmethionine by DNA methyltransferases (DNMT1 for maintenance of methylation patterns and DNMT3A and DNMT3B for de novo methylation activity) (Figure 1). Strikingly, CpG sites occur with a much lower frequency than expected due to random chance and unequally distributed across the human genome, leading to large low-density CpG regions interlarded with high CpG density short regions, denominated CpG islands (6). Around 60-70% of mammalian genes have CpG islands in the main regulatory region for gene transcription, known as proximal promoter. It has been well established that global DNA hypomethylation has been associated with genome instability and chromosome fragility and it is also accompanied with tumor suppressor gene silencing by hypermethylation of CpG islands (7) and their flanking regions called CpG shores (8).

Histones (H2A, H2B, H3, H4, and the linker H1) and the 146 bp of DNA wrap around the core of histones form the tridimensional basic particle called nucleosome to maintain the chromatin structure. Histones are chemically modified by different enzymes at external N- and C-terminal tails as well as at internal histone-fold domains, mainly consisting of acetylation, methylation, phosphorylation, and carbonylation, Histone modifications are considered epigenetic modifiers because they can induce changes in the state of the chromatin by changing the nucleosome structure and spreading to different regions of the chromatin. In fact, histones have been proposed as metabolic sensors, converting changes in metabolism into stable patterns of gene expression (5). Moreover, the key implication of histones, their PTMs and the identification of histone variants in the regulation of gene regulation has increased the enthusiasm for investigating the role histones in disease. Consistent with this notion, aberrant patterns of histone PTMs have been found in a large number of human malignancies (9).

Around 90% of the whole human genome is transcribed in a set of overlapping transcripts that do not codify any protein, these transcripts are known as non-coding RNAs. There have been described different types of ncRNA but the most studied one are the microRNAs (miRNAs). miRNAs are a large family of short non-coding RNAs (17-25 nucleotides) (10), involved in many biological processes, such as cellular development, differentiation, apoptosis, and proliferation (11), but also in human pathologies like Alzheimer, cardiovascular disease and cancer (12). At present, It is estimated that as many as 30% of mammalian genes are regulated by miRNAs and around 1,600 human precursor miRNA sequences and 2,042 mature miRNA sequences have been recorded in the miRBase (http://www.mirbase.org) (13), but the number is rapidly growing. Moreover, microRNAs negatively regulate gene expression mainly by the disruption of the protein translational initiation in the ribosome (14).

Genome-wide association (GWA) studies are unraveling the molecular mechanisms underlying the interaction between transcription factors, coregulators, and the basal machinery. On top of that, the epigenetic landscape adds a higher level of complexity. The hypothesis of the histone code describes the chromatin signaling pathway in which chromatin is regulated in an open/closed state depending on PTMs (15, 16). Nevertheless, histone modifications have context-dependent effects, making their interplay comparable to the complexity of a "language". The increasing number of conserved histone PTM and their context-dependent effects has coined the concept of epigenetic language *versus* epigenetic code (17, 18). Regarding DNA methylation, global hypomethylation occurs mainly at repetitive sequences, promoting chromosomal instability, translocations, gene disruption (19). However, hypermethylation at specific CpG islands in the promoters provokes transcriptional inactivation of genes involved in DNA repair, cell cycle control, the p53 network and apoptosis among others (20). In gene silencing directed by RNA interference (RNAi), the relevance, nature and extend of the non-coding RNAs (ncRNAs) have emerged as key elements of cellular homeostasis (21) (12).

The epigenetic modifications, and the underlying molecular mechanism, establish an additional level of regulation in which metabolic pathways and transcriptional networks are intertwined in response to developmental and environmental cues, thus sensing changes in the concentrations of intracellular metabolites during hormonal or nutrient signaling (22).

4. METABOLIC SENSORS AND TRANSCRIPTIONAL COREGULATORS

A compelling body of evidence accumulated in recent years supports the hypothesis that almost all chromatin-modifying enzymes sense the concentration of metabolites and therefore the metabolic status of the cell, organ or organism. These metabolites act as endogenous co-factors or substrates regulating the enzymatic activity of chromatin regulators. Thus, changes in the concentration of the intermediary metabolites may change the activity of the chromatin regulators leading to a homeostatic transcriptional response (Figure 1) (5, 23-27).

Amongst the most studied metabolites the acetyl-CoA, nicotinamide adenine dinucleotide (NAD+), adenosine thriphosphate (ATP), ATP S-adenosylmethionine (SAM) and flavin adenine dinucleotide (FAD) have prevailed, meanwhile other metabolites such as uridine diphosphate (UDP)-glucose, a-ketoglutarate (a-KG) have recently raised their importance in post-translational modifications and cancer progression (28, 29) (30, 31).

A very interesting question arises when considering how the endogenous rhythms are coupled with cellular environments and why circadian desynchrony leads to metabolic pathologies (32). Current lifestyle is affecting the circadian rhythms leading to different kind of pathological conditions including sleep disturbances, depression, and it might lead to increased susceptibility to cancer as observed in humans working night shifts (33) (34). The molecular mechanisms that couple metabolism to circadian oscillators are just emerging (35). CLOCK and BMAL1 are the positive regulators of the mammalian clock machinery directing the expression of several nuclear receptors which act as sensors for metabolites and xenobiotics (36). Interestingly, clock/clock mutant mice, which are arrhythmic when placed in constant darkness, become hyperphagic and obese, and develop classical signs of metabolic syndrome such as hyperglycaemia, dyslipemia and hepatic steatosis (fatty liver) (37). Moreover, loss of BMAL1, which renders mice completely arrhythmic (38), also leads to disruption of oscillations in glucose and triglycerides levels (39).

The core of transcriptional components of the clock machinery involves the transcriptional-translation feedback loop in which the transcription factors CLOCK and BMAL1 activate the Period (*Per1, Per2, Per3*) and Cryptochrome (*Cry1, Cry2*) genes via E box enhancer sequence elements in their promoters (40). Circadian clock proteins engage in additional functions when they collaborate with proteins outside of the core clock machinery. While CLOCK:BMAL1 activate numerous clock output genes, CRY1 and PER proteins bind to other nuclear receptors or intracellular proteins to regulate disparate functions such as adipogenesis and gluconeogenesis (41). However, less is known about posttranslational modifications (PTMs) of the core components of the circadian clock and its contribution to lipid homeostasis in the liver. Several PTMs are highly sensitive to nutrient availability. Two NAD^+-dependent protein enzymes, SIRT1 deacetylase and PARP1 ADP-ribosyltransferase, were shown to bind to the CLOCK-BMAL1 complex and affect its DNA binding activity and target gene expression (42) (43). Other signaling proteins such as the energy-responsive AMP-activated protein kinase (AMPK) phosphorylate and facilitate the degradation of CRY1 (44). Nutrient sensors such as mTOR and AKT were also shown to link metabolic signals to the circadian systems (45). In this context, CLOCK/BMAL1 and PER/CRY complexes interact with several histone modifiers, for the rhythmic assembly and recruitment to chromatin of multiprotein complexes in a circadian time-dependent fashion. The protein CLOCK itself has histone acetyl-transferase (HAT) activity, acetylating its own transcriptional partner BMAL1 (46). The methyltransferase mixed lineage leukemia 1 (MLL1) also interacts with CLOCK, and EZH2 methylates histones on the circadian promoter. Other histone demethylases such as Jarid1A and JMJD5 participate in the maintaining

the circadian epigenome, and specifically in the liver, the histone deacetylase HDAC3 and its coactivator NCoR are recruited to chromatin via the nuclear receptor REV-ERBα which has been defined as an integral component of the circadian clockwork machinery and represent a direct molecular link between circadian outputs and lipid metabolism (47) (48).

Recently in 2013, Kaasik *et al.* and Li *et al.*, have shown that the hexosamine/O-GlcNAc pathway modulates peripheral clock oscillations. O-GlcNAc transferase (OGT) promotes expression of BMAL1/CLOCK target genes and affects circadian oscillations of clock genes *in vitro* and *in vivo*. The addition of b-D-N-acetylglucosamine (GLcNAc) on BMAL1 and CLOCK inhibits ubiquitination and degradation of these proteins, and mice with perturbed hepatic OGT expression show aberrant circadian rhythms of glucose homeostasis (28, 29). High glucose stimulates the activity of MLL5 through increased GlcNAcylation linking the activity of histone-modifying enzyme directly to the extracellular concentration of glucose (49).

5. EPIGENETIC STATE AND HUMAN METABOLIC DISEASES

Caloric restriction and time-feeding restriction have a key role in regulating fatty liver and metabolic disorders through epigenetic mechanisms (50) (51) (52, 53) (41). Furthermore, recent discoveries about how epigenetic marks are stably inherited by transgenerational inheritance highlight the importance of unraveling the epigenetic mechanisms associated with cholesterol and lipid homeostasis (54) (55). Additionally, another factor to take into account is exercise because it ameliorates metabolic dysfunction and prevents chronic disease throughout epigenetic remodeling (56) (57, 58). At present, the impact of exercise and nutrition on the tissue-specific epigenetic profile remains on debate (59).

Several metabolic diseases have been characterized by GWA approaches and in some cases the genetic risk loci identified account for less than 10% of the observed heritability such as in type 2 diabetes mellitus (T2DM). These results in combination with the maternal and paternal inheritance of susceptibility, supports the role of epigenetics in the development of T2DM (60-62). The Dutch famine study is an emblematic example of environmental influences on the epigenome leading to obesity and T2DM in the offspring (63). In the end of the Second World War II, the Western Netherlands was plagued by an acute famine for 6 months. Pregnant mothers affected by the famine during the first two trimesters gave birth to children more prone to become obese than children born to mother who experienced famine at a later pregnancy stage or not exposed at all (63). Later on, studies using animal models provided evidence that undernutrition during pregnancy causes intrauterine growth retardation (IUGR) which predisposes the offspring to develop metabolic aberrations, such as obesity and T2DM (54, 55, 64, 65). Recently, Wei et at., have shown by using a non-genetic prediabetic mouse model that environmentally induced epigenetics alterations in sperm can be inherited to the next generation (62). A large proportion of genes associated with insulin and glucose metabolism were down regulated in the pancreatic islets of the offspring (62). Albeit changes in cytosine methylation did not globally correlate with changes in gene expression, substantial changes were detected in the intragenic regions of *Pik3r1* and *Pik3ca* (62), and this indicate the importance of epigenetic regulation in the gene chromatin-context. In particular, the epigenetic regulation of the peroxisome the proliferator-activated receptor γ coactivator-1α (*Pgc-1α*) emphasizes its central role as metabolic master regulator in different metabolic organs such as pancreas, liver and muscle, being exercise a recommended lifestyle intervention for preventing metabolic dysregulation (57, 66).

6. NON-ALCHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of conditions associated with the over-accumulation of lipids in the liver, ranging from steatosis to non-alcoholic steatohepatitis (NASH), which is characterized by the accumulation of fat in the liver along with evidence of liver cell damage, inflammation and different degrees of fibrosis. The prevalence of both NAFLD and the metabolic syndrome has increased dramatically worldwide becoming a social challenge (67). Moreover, there is an increasing number of evidence where NAFLD is associated with obesity, insulin resistance, hypertension, dyslipemia and metabolic syndrome. Indeed, NAFLD is considered a manifestation of metabolic syndrome and therefore linked to the development of obesity and insulin resistance (68). Two social considerations must be taken into account. First, the rapid spread of the obesity 'pandemia' in adults and children (69). Secondly, the prevalence of the metabolic syndrome and NAFLD in humans increases with ageing (70). In 20- to 29-year-olds the prevalence is 7% but rises to 44% in individuals aged 60-69 years (70). Similarly, ageing has also been shown to be a risk factor for the development of human NAFLD (71) (72).

In NAFLD, the first therapeutic approach starts with diet and lifestyle intervention to improve insulin sensitivity. When the pathology becomes more aggressive a pharmacological treatment is included, but in many cases after drug discontinuation, liver enzymes worsened indicating the need for long-term use of drugs despite there are no significant improvement in NAFLD progression associated with the pharmacological treatment. In general, there is no consensus on the best way to manage Non-alcoholic Steatohepatitis (NASH) (73).

In the liver, lipid homeostasis regulation is achieved by the action of hormones, like insulin, or intracellular metabolites, notably fatty acids and sterols, that can activate transcription factors, including nuclear hormone receptors (PPARα, PPARg, LXR), the carbohydrate response element binding protein ChREBP, the sterol regulated factor SREBP1c, and the PPARa coactivator PGC1α which integrates metabolic and clock signals. The nuclear receptors PPARα and PPARg are key regulators of genes encoding proteins involved in fatty acid uptake, storage and degradation. PPARα and PPARg ligand-dependent activation provides the principal mechanisms for sensing changes in the concentrations of intracellular metabolites during hormonal or nutrient signalling (22). Remarkably, PPARα binds to the *Bmal1* promoter to modulate its expression and in turn, PPARα expression is regulated by CLOCK-BMAL1 through E-boxes present in its own promoter (74). The coverage of circadian regulation involves a temporal mRNA expression profiling of all 45 nuclear receptors in various metabolic tissues (75).

The insulin resistance (IR) traits and the promoter methylation of PGC1α have been correlated in human biopsies from NAFLD patients showing that promoter DNA methylation inversely correlates with the abundance of PGC1α mRNA (76). Although there are no evidence suggesting a global DNA methylation pattern associated with NAFLD, it has been described in promoter regions, that changes in the DNA methylation level of several liver-specific regulators of the lipid homeostasis correlate with liver fatty acid content (54, 55, 76). Several approaches argue in favor of DNA methylation as a key epigenetic modification involved in glucose and lipid metabolism. The first epigenome wide association study (EWAS) was conducted in human blood comparing the DNA methylation and metabolic traits (metabotypes) from 1814 participants (77). Lipid-parameters and environmental factors were also included although the study considers several limitations. For instance, the DNA methylation is a readout from a mixture of different cell types obtained from whole blood and the blood metabolites levels are produce in peripheral tissues such as liver, kidney, muscle and adipose tissue (77). Additional studies focused on the T2D epigenetic networks including non-fatal metabolic alterations describe the interplay between DNA methylation and chromatin modifications in genes that could affect the development of T2D (78). Another example of epigenetic regulation involved in the NAFLD phenotype is sustained by the correlation of the lipid accumulation and inflammation in the liver, with the downregulation of the Polycomb Group protein Enhancer of Zeste Homolog 2 (EZH2) which trimethylates the lysine 27 on the histone H3 (79)

In summary, PTMs triggered by lipid accumulation coordinate a set of pathways and networks with the main objective of keeping energy homeostasis at different cellular and systemic levels. Glucose and lipid metabolism are closely intertwined through rate-limited enzymes, metabolites that act as ligand, common transcriptional regulators, circadian clocks and hormonal signalling between central and peripheral organs such adipose, muscle tissue, liver and pancreas. Prevalence and severity of NAFLD has paralleled that obesity, T2DM and the metabolic syndrome leading us to consider the significance of the fine-tuned crosstalk between insulin resistance and fatty liver.

7. SUMMARY AND PERSPECTIVES

Genome-scale base-resolution studies of DNA methylation patterns have recently revealed the dynamics of cytosine methylation during early developmental stages. Imprinting control regions (ICRs) can be classified into germ-line ICRs (gICRs) and somatic ICRs (sICRs). The allele-specific methylation of gICR is established during gametes development and is maintained after fertilization, while in sICRs is set up during mammalian development after fertilization and in a tissue-specific manner (80). The classical model postulates that at fertilization, paternal DNA is actively demethylated and the maternal DNA is passively demethylated (81). In contrast, Wang *et al*. have shown that paternal methylome and a significant proportion of maternal methylome undergo active demethylation during embryonic development (82). Therefore, modifications triggered early in life may have a great phenotypic effect as they are amplified by cellular replications and cell fate decisions occurring during development (83). But, are these modifications phenotypically transmitted displaying a short-term rather than a long-term transgenerational effect over multiple generations? (84)

Maternal and paternal nutrition are critical determinants of adult offspring health. Since metabolic risk can be inherited to subsequent generations even in the absence of further environmental stressors, the transgenerational epigenetic inheritance arise as a mechanism to explain complex traits and metabolic programs (54) (55) (85, 86). Transgenerational effects relay on the fact that epigenetic marks are inherited over multiple generations, and effects from parental or grandparental origin may influence their offspring in many ways, for instance, by nutritional and hormonal information during embryogenesis, or contributing with bioactive molecules in the egg (85, 87) and sperm cytoplasm (54, 55). The quantification in the plant *Arabidopsis thaliana* of epialleles, epigenetic variants that cause a phenotype with the same DNA sequence but different DNA methylation patterns, has provide strong evidence to support that epialleles contribute to the heritability of complex traits (88). The analysis on experimentally generated epigenetic recombinant inbred lines (epiRILs) derived from crosses with *decreased in dna methylation 1-2* mutant (*ddm1-2*) as compared with

wild type plants have shown that differentially methylated regions (DRMs) in the epiRIL are stable at least during seven generations (88). In mammals, multigeneration effects of poor maternal nutrition cause alterations in lipid metabolism of F2 generations offspring when male mice were expose to intrauterine growth restriction (IUGR) (87). At least in part, altered DNA methylation in the 5' UTR of the key lipogenic transcription factor liver X receptor-alpha (*Lxra, Nr1h3*) correlated with its expression profile, and this epigenetic signature was found in the sperm of the F1 progenitors, and the somatic cells of the F2, in the fetal and adult liver and skeletal muscle, suggesting that altered lipid metabolism is transmitted to subsequent generations through modifications in epigenetic marks in gametes (87).

In order to identify the parts of the genome that are most susceptible to perturbation by environment exposures, genome-wide methylation studies for quantitative comparisons represent a handicap taking into account that each cell type has a distinct methylome and that a reference methylation data sets is needed. Conventional analysis of the genome of any mammalian tissue that is carried out with supposedly phenotypically homogenous populations, typically with thousands or millions of cells analyzed in bulk, simply cannot capture the inter-cellular heterogeneity present in certain tissues, including developmental stages or cellular responses to internal or external cues (89), and therefore changes in the order of 2%-5% might not be detected (87).

The presence of multiple cell clones with distinct genotypes in the same individual is referred to as *somatic mosaicism*. One of the major challenges for understanding the maternal health repercussions on the metabolic health of offspring and subsequent generation is to be able to discern the epigenetic regulatory modifications that may be transmitted through gametes or acquired during life span. Somatic tissues are mosaics of genotypes and the severity of the mutation load of a particular tissue, determines the likelihood of functional decline, taking into account that even low-abundance mutations can cause organ or tissue dysfunction.

During the past two decades, genetic linkage-based studies have proved very useful as providers or biomarkers for diagnosis, patient stratification and prognostic or therapeutic categorization in Mendelian (single gene) disorders (90). However, this approach is not applicable for studying complex traits. In order to bypass this limitation, GWA studies have the potential to identify the genetic variants associated with multifactorial disorders and aged-related diseases. Advances in next-generation sequencing and bioinformatics already permits high-resolution screening of a single-cell genome, transcriptome and epigenome (91-93). Single-cell analyses are already routinely used for pre-implantation diagnosis and it is foreseen that they will provide unanticipated novel therapeutic approaches for personalized medicine.

Chromatin modifying enzymes utilize substrates or co-factors generated by cellular metabolism, thereby providing a potential link between nutrition, metabolism, and gene regulation. Dynamic PTMs in chromatin associated and non-associated enzymes sense metabolic signals orchestrating fine-tuned transcriptional programs for coordinating homeostatic responses or determine cell fate decisions during development or differentiation programs. Compelling evidence place the epigenome as the key 'missing piece' or 'missing' heritability in complex phenotypes contributing to build an emerging field of 'epigenetic epidemiology' emphasising the importance of establishing a causal role in pathology for disease-associated epigenetic changes (94).

Additionally, epigenetics might be decisive to identify interindividual variability in drug metabolism and transport. Direct variations in the regulatory and coding regions of absorption, distribution, metabolism and excretion (ADME)-related genes such as *CYP3A4 gene* (95), as well as in transcription factors such as pregnane X receptor and constitutive andostrane receptor contribute to interindividual variability in ADME gene expression and function (96). A novel field of pharmacoepigenetics is targeting the importance of adverse drug reactions (ADRs) which cannot be explained by genetic factors (97) (98).

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