

Epigenetic Regulation and Its Implications in Inborn Errors of Metabolism: A Review

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Abstract

Inherited metabolic diseases (IMDs) are a varied collection of genetic disorders resulting from enzyme deficiencies, transporter or co-factor of metabolic pathways. The traditional view has been that the pathophysiology of IEMs is the consequence of genetic abnormalities affecting normal metabolic pathways, resulting in the buildup of harmful metabolites or shortage of necessary products. However, an increasing body of research suggests that genetic mutations alone may not account for the heterogeneity in disease severity, age of onset, treatment response and clinical prognosis observed among affected persons. Epigenetic control has consequently become a key aspect regulating the phenotypic expression of many illnesses. Epigenetics is the study of heritable, reversible changes in gene expression that are not due to changes in the DNA sequence. These changes include DNA methylation, histone modifications and chromatin remodeling, as well as control by non-coding RNAs. The intimate connection between metabolism and epigenetics has become more evident, as many metabolic intermediates are substrates or cofactors for epigenetic enzymes. Thus, the metabolic derangements typical of IEMs might lead to global epigenetic modifications that affect cell differentiation, organ development, immunological responses and disease progression. In contrast, epigenetic dysregulation can alter the expression of genes involved in metabolic pathways, leading to complicated interactions between genetic and environmental variables. Recent breakthroughs in next generation sequencing, epigenome wide association studies, and multi-omics technologies have expanded our understanding of the molecular mechanisms underlying the relationship between metabolism and epigenetics. These findings have also opened the door for biomarker discovery, better diagnosis, prognosis prediction and new treatment approaches targeting reversible epigenetic alterations. Despite substantial advances, problems still need to be addressed, such as the paucity of diseasespecific epigenetic data, tissue-specific epigenetic variation and the unknown safety profile of epigenetic therapeutics in the long run. Here we discuss basic mechanisms of epigenetic regulation, the relationship between metabolism and epigenome, current evidence on epigenetic alterations in selected inborn errors of metabolism and their diagnostic, therapeutic and future clinical implications.

Keywords: Epigenetics; DNA methylation; Histone modification; Non-coding RNA; Inborn errors in metabolism; Metabolomics; Precision medicine

Introduction

Inborn errors of metabolism (IEMs) are a heterogeneous collection of inherited genetic diseases originating from defects in enzymes, transport proteins, receptors or cofactors that are important for metabolic pathways. Since Sir Archibald Garrod first described alkaptonuria as a “inborn error of metabolism” in 1908, there have been remarkable advances in molecular genetics that have identified over 1,700 distinct metabolic disorders involving

carbohydrate, amino acid, lipid, vitamin, purine, pyrimidine, mitochondrial, lysosomal and peroxisomal metabolism. These illnesses are uncommon as independent entities, but collectively they are a major cause of newborn morbidity, developmental impairment and early mortality globally [1,2]. The clinical presentations of IEMs range from severe neonatal metabolic crises to milder adult-onset symptoms. Patients with the same pathogenic variations can differ markedly in the severity of disease, the course of disease and the responsiveness to therapy. The diversity might

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suggest that other processes in addition to DNA sequence alterations are involved in disease expression [3]. Epigenetic regulation is among the most important processes regulating gene activity without changes in nucleotide sequences. Epigenetic mechanisms include DNA methylation, histone modification, chromatin remodelling and regulation by non-coding RNAs. These processes regulate gene expression throughout embryonic development, tissue differentiation, cellular metabolism, ageing, and responses to environmental stimuli [4]. Unlike genetic mutations, epigenetic alterations are dynamic and can be reversible. Epigenetic processes can be influenced by nutritional status, environmental exposures, oxidative stress, inflammation, and intracellular metabolite concentrations. This dynamic character has received increasing interest as it offers options for therapeutic intervention [5]. Of particular relevance in IEMs is the interplay between metabolism and epigenetics. Many metabolites created during normal metabolism, including as acetyl-CoA, S-adenosylmethionine (SAM), α -ketoglutarate, nicotinamide adenine dinucleotide (NAD⁺) and flavin adenine dinucleotide (FAD), are important cofactors for enzymes that modify DNA and histones. Thus, metabolic abnormalities typical of IEMs may result in direct modifications of the epigenetic landscape, leading to extensive changes in gene expression [6]. For instance, aberrant accumulation of organic acids in organic acidemias, increased phenylalanine in phenylketonuria (PKU) or defective mitochondrial oxidative phosphorylation may alter DNA methylation patterns, histone acetylation, mitochondrial biogenesis and inflammatory pathways. These subsequent epigenetic changes may contribute to neurological impairment, cognitive dysfunction, immunological dysregulation and disease progression independent of the initial genetic abnormality [7]. Recent breakthroughs in high-throughput sequencing, epigenome-wide association studies (EWAS), transcriptomics, metabolomics and single cell technologies have increased our understanding of these complicated connections. Integration of genetic and epigenomic information has become increasingly crucial in precision medicine, enabling researchers to uncover novel biomarkers and individualised treatment targets [8]. The present study intends to provide a broad perspective on epigenetic regulation and its implications in the development, diagnosis and management of inborn errors of metabolism. The bidirectional crosstalk between metabolic pathways and the epigenetic mechanisms, recent advances, and future therapeutic potential are highlighted.

Inborn Errors of Metabolism: A General Overview

Inborn errors of metabolism are a wide and ever-growing collection of inherited diseases caused by mutations affecting enzymes, transporters, cofactors, receptors or structural proteins involved in intermediary metabolism [1]. Most IEMs are

individually rare, occurring between 1 in 10,000 and less than 1 in 1,000,000 live births. However, collectively they occur in about 1 in every 800-2,500 babies, depending on the community investigated and the extent of newborn screening programs [2]. Most IEMs are inherited as autosomal recessive traits, however autosomal dominant, X-linked and mitochondrial inheritance have been documented. Clinical signs may occur in foetal development, the neonatal period, childhood or adulthood depending on the metabolic pathway involved, residual enzyme activity, environmental variables and modifier genes [3].

In-Ear-Monitors are usually divided into three main categories

Intoxication disorders, such as amino acid disorders (phenylketonuria, maple syrup urine illness), organic acidemias, and urea cycle disorders, are characterised by the accumulation of toxic metabolites. Disorders of energy metabolism, including mitochondrial illnesses, fatty acid oxidation deficiencies and glycogen storage diseases are characterised by a defective ATP synthesis. Disorders of complex molecules, such as lysosomal storage illnesses, peroxisomal disorders, congenital disorders of glycosylation, and cholesterol biosynthesis disorders, can impact macromolecule production or destruction [2]. Recent progress in tandem mass spectrometry and increased newborn screening has transformed the early diagnosis and treatment of many IEMs. Improved survival for many individuals has been achieved with early dietary management, enzyme replacement therapy, substrate reduction therapy, vitamin supplements, and liver transplantation. However, even with treatment, neurological damage is still widespread and suggests that there are other biological pathways involved in illness progression [2,8]. There is increasing evidence that metabolic aberrations not only have direct biochemical implications but also affect many cellular signalling pathways. Long-term accumulation of metabolites can lead to oxidative stress, mitochondrial dysfunction, inflammatory responses, alterations in chromatin organization and epigenetic remodelling. Such secondary modifications might alter the expression of genes not involved in the original mutation, so increasing the severity of the disease and adding to phenotypic heterogeneity [6]. Maternal nutrition, illnesses, drugs, physical activity and nutritional therapy are among the environmental factors that can also affect epigenetic regulation throughout life. These interactions may, in part, explain the common presence of quite varied clinical symptoms in patients with the same mutation, highlighting the significance of combining genetics and epigenetics for the understanding of the aetiology of IEMs.

Basics of Epigenetic Regulation and Main Epigenetic Mechanisms

The study of changes in gene expression that are heritable and reversible but are not due to changes in the DNA sequence itself. These changes control when, where and how much genes are expressed, and influence cellular differentiation, development, adaptability to environmental stimuli and susceptibility to illness. The major players in epigenetic control are DNA methylation, histone alterations, chromatin remodelling and non-coding RNAs [4,9]. Unlike genetic mutations, epigenetic alterations are dynamic and are subject to intrinsic and external causes. Nutrition, ageing, oxidative stress, inflammation, pollutants, drugs and lifestyle can all affect the epigenetic landscape. This plasticity allows cells to adapt to changing environmental situations while preserving stable gene expression patterns necessary for appropriate physiological activities [5]. The crosstalk between metabolism and epigenetics is especially important because many metabolic intermediates are substrates or cofactors for enzymes that regulate epigenetics. For example, S-adenosylmethionine (SAM) serves as the universal methyl donor for DNA and histone methyltransferases, whereas acetyl-coenzyme A (acetyl-CoA) provides acetyl groups needed for histone acetylation. Similarly, α -ketoglutarate, nicotinamide adenine dinucleotide (NAD⁺) and flavin adenine dinucleotide (FAD) and succinate modulate the activity of a number of chromatin-modifying enzymes [6]. Inherited enzyme defects that prevent the generation or use of these metabolites, termed inborn errors of metabolism, result in biochemical abnormalities and also in secondary epigenetic changes. Thus, aberrant metabolite buildup could lead to altered global gene expression, influencing disease development, organ dysfunction and variation in clinical presentation [7]. Recent developments in epigenomic profiling revealed that several of the IEMs show altered DNA methylation signatures, patterns of histone modifications, and expression profiles of microRNAs. These findings indicate that epigenetic dysregulation is a pivotal mechanism linking metabolic disorders and pathologic phenotypes [8].

Significant Mechanisms of Epigenetic Regulation

The most researched epigenetic mechanism is DNA methylation. It is the addition of a methyl group to the fifth carbon of cytosine in CpG dinucleotides and is catalysed by DNA methyltransferases (DNMT1, DNMT3A and DNMT3B) with SAM as the methyl donor [9]. In general, promoter methylation inhibits transcription factor binding and recruits proteins that induce chromatin condensation, hence repressing gene transcription. Hypomethylation, on the other hand, is often associated with gene up-regulation and genomic instability [10]. DNA methylation is critical for embryonic development, genomic imprinting, X-chromosome inactivation, chromosomal integrity maintenance and tissue specific gene expression. Changes in methylation patterns

have been linked to various diseases including cancer, neurodevelopmental problems, cardiovascular disease and inherited metabolic abnormalities [4]. Disruptions in onecarbon metabolism in IEMs may directly alter DNA methylation. Defects in methionine metabolism, folate metabolism or vitamin B12-dependent pathways alter intracellular levels of S-adenosylmethionine (SAM), which in turn modify methylation capability and affect the expression of many genes other than those directly affected by the underlying mutation [6]. Studies of phenylketonuria have also described altered methylation patterns in the presence of chronic hyperphenylalaninemia, suggesting that sustained metabolite buildup may lead to secondary epigenetic alterations that contribute to neurological dysfunction [7]. DNA is wound around histone proteins to create nucleosomes, the primary structural units of chromatin. Post-translational changes such as acetylation, methylation, phosphorylation, ubiquitination, SUMOylation and ADP-ribosylation modify histone tails in several ways. Such changes alter chromatin accessibility and gene transcription [10]. Histone acetyltransferases (HATs) catalyse the transfer of acetyl groups from acetyl-CoA to lysine residues of the histone tails. Acetylation removes the positive charge on histones, weakening the link between histones and DNA, relaxing the chromatin structure, and promoting active gene transcription [11]. In contrast, histone deacetylases (HDACs) catalyse the removal of acetyl groups resulting in chromatin condensation and transcriptional suppression. Cellular energy metabolism also affects HDAC activity, especially NAD⁺-dependent sirtuins that function as metabolic sensors to link nutrition availability with gene regulation [12]. Histone methylation is more complex as methyl groups can be added to lysine or arginine residues resulting in either transcriptional activation or repression depending on the amino acid residue changed. Histone methyltransferases use SAM as methyl donor, whereas demethylases frequently require α -ketoglutarate as cofactor [10]. Acetyl-CoA, NAD⁺ and α -ketoglutarate are products of intermediate metabolism and, hence, metabolic abnormalities in IEMs may have dramatic effects on histone alterations. Altered histone acetylation and methylation have been linked to mitochondrial dysfunction, oxidative stress, poor neural differentiation and inflammation found in a number of hereditary metabolic illnesses [6].

Chromatin remodelling is the ATP dependent change in structure that controls nucleosome placement and DNA accessibility. Chromatin remodelling complexes, including the SWI/SNF, ISWI, INO80 and CHD families, reposition or evict nucleosomes to promote or inhibit transcription [9]. These remodelling complexes cooperate with DNA methylation and histone changes to specify tissue-specific transcriptional pathways. Proper chromatin remodelling is critical for embryogenesis, neural differentiation, immunological function and metabolic adaption. Metabolic stress

typical of IEMs might impact on the availability of ATP, the formation of reactive oxygen species and intracellular signalling pathways, and hence change chromatin remodelling activity. Then, impaired chromatin dynamics could influence genes related to mitochondrial biogenesis, antioxidant defence, inflammation and cellular stress responses [13]. Chromatin remodelling has been less studied in IEMs compared to DNA methylation or histone modifications. However, there is increasing evidence that abnormal chromatin organization is involved in disease progression, especially in mitochondrial disorders and lysosomal storage diseases [13]. A small fraction of the human genome is coding for proteins, whereas the rest is translated into non-coding RNAs (ncRNAs). These molecules influence gene expression at the transcriptional and post-transcriptional level without coding for proteins [14]. MicroRNAs (miRNAs) are small non-coding RNAs of around 22 nucleotides in length that bind to corresponding sequences in the messenger RNAs leading to mRNA destruction or translational repression. Individual miRNAs can target hundreds of genes at once and are thus strong regulators of cellular metabolism, proliferation, apoptosis and differentiation [14]. Long non-coding RNAs (lncRNAs) are RNAs longer than 200 nucleotides that affect chromatin architecture, recruitment of transcription factors, RNA processing and activity of epigenetic enzymes. Circular RNAs (circRNAs) have also been identified as significant regulators by interaction with miRNAs and RNA-binding proteins. Recently, aberrant miRNA expression profiles have been reported in some hereditary metabolic diseases. Dysregulated miRNAs have been implicated in mitochondrial dysfunction, hepatic steatosis, neurodegeneration, inflammation and oxidative stress associated with IEMs [15]. Circulating miRNAs are quite stable in biological fluids and have been studied as potential non-invasive biomarkers for diagnosis, disease monitoring and therapy response. Moreover, therapeutic manipulation of miRNA activity, via miRNA mimics or inhibitors, is a promising field of translational research [15].

Metabolism-Epigenetics Crosstalk

One of the most important findings in current molecular biology is the close connection of metabolism and epigenetics. Metabolic pathways are not isolated, but rather offer substrates, cofactors and energy for epigenetic alterations, while epigenetic mechanisms control the expression of metabolic enzymes and transporters [6]. Some of the important metabolites that exhibit this are:

S-adenosylmethionine (SAM): the universal methyl donor for DNA and histone methylation. Acetyl-CoA: a key metabolite and second messenger. α -Ketoglutarate: cofactor for DNA and histone demethylases NAD⁺: needed for sirtuin deacetylase activity.

FAD: co-factor of lysine-specific histone demethylases. Changes in intracellular concentrations of these metabolites, as is frequently

encountered in IEMs, can significantly impact chromatin architecture and global gene expression. This bidirectional link gives a molecular explanation for why metabolic diseases commonly involve numerous organ systems despite a deficiency in a single enzyme [6]. The discovery of this metabolism-epigenetics axis has expanded the study of inherited metabolic illnesses beyond traditional biochemical models and opens up new possibilities for biomarker identification and the development of tailored therapy strategies.

Epigenetic Modifications in Some Inborn Errors of Metabolism

Clinical relevance of epigenetic dysregulation in IEMs

Epigenetic changes could explain the considerable clinical variation reported in patients with the same causal mutations. Changes in DNA methylation patterns, histone modifications and microRNA expression may affect the remaining enzyme activity, inflammatory responses, neural resilience and sensitivity to environmental stresses [5].

Several major clinical consequences have been highlighted

Phenotypic variability: The heterogeneity in disease severity and age of onset among patients with the same mutation could be due to epigenetic variations.

Disease progression: Persistent epigenetic changes may still contribute to organ damage even after pharmacological treatment.

Biomarkers: DNA methylation patterns and circulating microRNAs are promising biomarkers for diagnosis and prognosis.

Precision medicine: Combining genetic, metabolomic and epigenomic data to enhance personalised treatment options. Therapeutic targeting: Because epigenetic alterations are reversible, they are ideal targets for innovative pharmacological therapies. The increasing understanding of these pathways underlines the relevance of include epigenetic research in the diagnosis and management of hereditary metabolic disorders. Development of multi-omics technologies will eventually lead to the identification of disease-specific epigenetic signals, which will further improve risk prediction, treatment monitoring, and personalised patient care [8].

Epigenetics for the Diagnostic Use in Inborn Metabolic Disorders

The traditional approach to the diagnosis of inborn errors of metabolism (IEMs) has relied on clinical examination, biochemical testing, enzyme assays and molecular genetic analysis. These approaches still underpin diagnosis, but frequently cannot account for the wide range in illness severity, treatment response and prognosis seen in individuals with the same genetic variations.

Recent breakthroughs in epigenetics have opened new avenues for improving the diagnosis and clinical management of many illnesses [8]. Epigenetic biomarkers are detectable changes in DNA methylation, histone modifications or non-coding RNA expression that represent disease linked biochemical changes. Unlike genetic abnormalities that are permanent throughout life, epigenetic markers are changeable and can provide information on disease activity, progression and therapeutic response [4]. Among many epigenetic pathways, DNA methylation is one of the most promising diagnostic indicators. In a number of hereditary metabolic illnesses, disease specific methylation signatures have been established and may augment standard biochemical and genetic investigations. Epigenome-wide association studies (EWAS) have shown distinctive methylation patterns related with metabolic failure, inflammation and neurodegeneration [9]. Circulating microRNAs (miRNAs) are also of rising interest due to their stability in plasma, serum, urine and cerebrospinal fluid. Altered expression of miRNAs has been linked with mitochondrial malfunction, oxidative stress, neuronal damage and inflammatory responses in numerous IEMs. These features make miRNAs appealing candidates as minimally invasive biomarkers that may help in diagnosis, prognosis and treatment monitoring [15]. High-throughput sequencing technologies have permitted genome-wide investigation of the human epigenome. Researchers are now able to analyse gene regulation with a detail never achieved before with techniques like as whole-genome bisulfite sequencing, chromatin immunoprecipitation sequencing (ChIP-seq), assay for transposase-accessible chromatin sequencing (ATAC-seq), and RNA sequencing [10]. Integration of epigenomic data with genomes, transcriptomics, proteomics and metabolomics will give a more complete picture of the causes of disease. These multi-omics techniques may discover pathogenic pathways that are not apparent by DNA sequencing alone and may increase diagnostic accuracy, especially in patients with atypical clinical presentations or variations of unknown relevance [8].

Epigenetic Regulation: Therapeutic Implications

Among the most notable advantages of epigenetic regulation is that epigenetic alterations, unlike genetic mutations, are theoretically reversible. Therefore, epigenetic therapies are promising new adjuncts to conventional therapy of hereditary metabolic diseases. Diet remains the mainstay of care for many IEMs such as phenylketonuria, maple syrup urine disease and homocystinuria. In addition to ameliorating metabolic imbalances, dietary interventions may potentially influence epigenetic regulation through altering the supply of metabolites that are required for DNA methylation and histone modifications. For example, proper consumption of folate, vitamin B12, vitamin B6, methionine and

choline supports one-carbon metabolism and normal S-adenosylmethionine (SAM) production, hence conserving the potential for DNA methylation [6]. Likewise, ketogenic diets, medium-chain triglyceride supplementation and specialised amino acid formulations may influence cellular acetyl-CoA and NAD⁺ levels, hence indirectly modulating histone acetylation and sirtuin activity. These data indicate that dietary treatment may mediate therapeutic advantages through both metabolic and epigenetic mechanisms. Histone deacetylase inhibitors (HDAC inhibitors) increase histone acetylation, resulting in a more open chromatin conformation and increased gene transcription. Several HDAC inhibitors have been shown to provide positive effects in animal models of neurodegenerative and metabolic illnesses by decreasing inflammation, improving mitochondrial function and increasing neuronal survival [11]. While the use of HDAC inhibitors in IEMs is still primarily experimental, they hold promise for addressing the aberrant gene expression linked to mitochondrial dysfunction and oxidative stress. Further studies are needed to evaluate their long-term efficacy and safety in people with hereditary metabolic diseases. Aberrant DNA methylation is involved in the disease aetiology of several IEMs, and therefore treatments able to change methylation patterns have been of substantial interest. Experimental ways to restore normal methylation status are being investigated using food supplementation or pharmacological regulation of DNA methyltransferases. However, as DNA methylation affects thousands of genes at the same time, specific treatment techniques are required to minimise the unwanted consequences on normal cellular function. Therapies targeting non-coding RNAs have been developed because to the rapid progress in RNA biology. Synthetic microRNA mimics, antisense oligonucleotides, and small interfering RNAs (siRNAs) are being explored for their ability to modulate gene expression in disease [15]. These technologies present significant prospects to address aberrant molecular pathways linked with hereditary metabolic disorders. RNA-based therapeutics represent an emerging field of precision medicine but their clinical use is still limited. Biomedical research has been revolutionised by the advent of CRISPR-Cas technology. Modified CRISPR systems can selectively turn gene expression on or off without modifying DNA sequences, in addition to repairing pathogenic DNA mutations. Such 'epigenome editing' permits targeted change of DNA methylation or histone acetylation at specific genomic sites [15]. Epigenome editing is in its infancy but has the potential to give highly specialised medicines with fewer off-target effects than traditional epigenetic medications.

Challenges and Limitations

Although the progress is amazing, there are still significant hurdles limiting the therapeutic application of epigenetics in hereditary metabolic illnesses. Second, many of the epigenetic changes are tissue specific. Because biopsies of the brain, liver or heart may not be possible, researchers commonly rely on peripheral blood samples that may not correctly reflect disease-specific epigenetic modifications. Second, it still remains challenging to separate primary epigenetic aberrations from secondary changes induced by disease progression. Many identified epigenetic changes might be adaptive reactions rather than causative causes. Thirdly, epigenetic alterations are regulated by several environmental factors such as age, diet, drugs, illnesses, exercise, and exposure to pollutants. Such variables obfuscate epigenetic studies interpretation and limit repeatability across populations. Another key constraint is that the number of patients available for research is quite minimal as each IEM is an individually unusual condition. Hence, many published research have small sample sizes, limiting statistical power and generalisability. Finally, pharmaceutical modification of epigenetic pathways may have off-target consequences, as epigenetic enzymes affect thousands of genes at once. Thus, careful investigation of long-term safety and specificity is required prior to a typical clinical application. The next decade will see a revolution in the diagnosis and therapy of hereditary metabolic illnesses by the use of the integration of genomics, epigenomics, transcriptomics, proteomics and metabolomics. Multi-omics methods will improve our understanding of the mechanisms that drive diseases and will help to discover personalised treatment targets [16]. Artificial intelligence and machine-learning algorithms are rapidly being used to analyse complicated epigenomic datasets to predict disease progression, treatment response and clinical outcomes. These computational methods could enable precision medicine by finding patient-specific genetic fingerprints. Single-cell sequencing tools are also enhancing our understanding of tissue-specific epigenetic regulations. Instead of studying complete tissues, researchers may now study individual cells, and so find cellular heterogeneity that was previously undetectable. Another potential direction is the detection of early epigenetic modifications in neonatal screening. Early intervention may significantly enhance long-term outcomes if disease-specific epigenetic biomarkers can be recognised prior to the development of irreversible organ damage [17].

Conclusion

Epigenetic regulation has become a major component in understanding the pathophysiology and clinical diversity of inborn errors of metabolism (IEMs). These disorders are caused by inherited genetic mutations affecting metabolic enzymes,

transporters or cofactors, but increasing evidence indicates that epigenetic mechanisms, including DNA methylation, histone modifications, chromatin remodelling and non-coding RNAs, are playing a significant role in disease onset, severity, progression and response to therapy. It is the intimate connection between metabolism and epigenetics that explains why perturbations in metabolic pathways result in extensive changes in gene expression. Metabolites, including S-adenosylmethionine (SAM), acetyl-coenzyme A (acetyl-CoA), α -ketoglutarate, nicotinamide adenine dinucleotide (NAD⁺), and flavin adenine dinucleotide (FAD), are crucial substrates or cofactors for enzymes that drive epigenetic changes. Metabolic derangements observed in IEMs may therefore result in epigenetic alterations which, in turn, contribute to neurological dysfunction, oxidative stress, mitochondrial malfunction, chronic inflammation and multisystem organ damage. A growing body of evidence from studies in phenylketonuria, homocystinuria, methylmalonic acidemia, propionic acidemia, mitochondrial diseases, glycogen storage diseases, lysosomal storage disorders and urea cycle disorders suggest epigenetic dysregulation as an important contributor in disease pathophysiology. These results shed light on why people with the same pathogenic variations often demonstrate striking disparities in disease severity and clinical outcomes. Advances in epigenomics, next generation sequencing and multi-omics technologies have opened new prospects for identification of novel biomarkers that can improve diagnosis, prognosis and treatment monitoring. Likewise, the reversibility of epigenetic alterations has sparked interest in novel treatment strategies, including nutritional epigenetics, histone deacetylase inhibitors, RNA-based therapies, and targeted epigenome editing. While these approaches remain mostly exploratory, they hold great promise for the future of precision medicine. Progress is good, but there are still many hurdles ahead. The therapeutic applicability is still limited by tissue-specific epigenetic variation, small patient population, environmental impact on epigenetic regulation and worry over specificity and long-term safety of epigenetic therapies. These issues will require collaborative multidisciplinary research integrating molecular genetics, metabolomics, bioinformatics and clinical medicine. In conclusion, epigenetic control is one of the main links between the genotype and phenotype in inherited metabolic illnesses. Further study on the interplay of metabolism and the epigenome is expected to increase understanding of disease causes, allow diagnosis at a more precocious stage and promote the development of more effective personalised therapeutics for individuals with inborn errors of metabolism.

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