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Review Article

The Mendelian disorders of chromatin machinery: Harnessing metabolic pathways and therapies for treatment

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ABSTRACT

The Mendelian disorders of chromatin machinery (MDCMs) represent a distinct subgroup of disorders that present with neurodevelopmental disability. The chromatin machinery regulates gene expression by a range of mechanisms, including by post-translational modification of histones, responding to histone marks, and remodelling nucleosomes. Some of the MDCMs that impact on histone modification may have potential therapeutic interventions. Two potential treatment strategies are to enhance the intracellular pool of metabolites that can act as substrates for histone modifiers and the use of medications that may inhibit or promote the modification of histone residues to influence gene expression. In this article we discuss the influence and potential treatments of histone modifications involving histone acetylation and histone methylation. Genomic technologies are facilitating earlier diagnosis of many Mendelian disorders, providing potential opportunities for early treatment from infancy. This has parallels with how inborn errors of metabolism have been afforded early treatment with newborn screening. Before this promise can be fulfilled, we require greater understanding of the biochemical fingerprint of these conditions, which may provide opportunities to supplement metabolites that can act as substrates for chromatin modifying enzymes. Importantly, understanding the metabolomic profile of affected individuals may also provide disorder-specific biomarkers that will be critical for demonstrating efficacy of treatment, as treatment response may not be able to be accurately assessed by clinical measures.

1. Introduction

Historically, most forms of intellectual disability (ID) have been considered untreatable; therefore, health providers and families have focussed on improving affected children's neurodevelopmental outcomes through a range of disability supports. Advances in genomic testing have enabled diagnosis of a specific genetic aetiology for many patients with ID, with the diagnostic yield approaching 60% in some cohort studies. In parallel, ongoing research aims to identify causal genes in the remaining undiagnosed individuals [1]. Further, reduced cost and improved access to genomic testing has enabled access to earlier genetic diagnosis, with research currently underway to demonstrate the efficacy of genomic newborn screening, this means that diagnosis via newborn screening may be possible in the near future [2–4]. The advent of specific and early diagnosis for genetic causes of ID creates new opportunities for therapeutic intervention [5]. Although parental views support the early diagnosis and intervention for rare diseases, there will continue to be unmet need if the diagnosis does not translate to an improvement in care [6].

To date, genomic studies into ID have identified causative single nucleotide variants in >1000 genes. Within this group, genes involved in discrete molecular pathways are overrepresented, particularly genes associated with metabolism. Other pathways associated with ID include those involved with molecular transport of metabolic substrates, nervous system development, RNA metabolism, transcription, mitochondrial function, cell cycle, synaptic function, chromatin machinery and microtubules [7,8]. For these groups of disorders, finding targeted treatments that improve neurodevelopmental and cognitive outcomes should be a priority.

Some genetic disorders with ID are already amenable to treatment

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and there has been a significant drive in the last decade to identify more of such conditions [9,10]. Many treatable intellectual disabilities are caused by biallelic genetic variants genes that encode metabolic enzymes. For these conditions, treatments have arisen largely from a strong biological understanding of affected metabolic pathways, enabling the application of a range of dietary and pharmaceutical-based treatments to detoxify metabolites, supplement deficient metabolites and cofactors, reduce metabolic substrates or replace dysfunctional enzymes via enzyme replacement or gene therapy [11]. For some of these conditions, such as phenylketonuria, early treatment in the postnatal period has prevented the development of intellectual disability [12]. To date, these treatments have targeted the modification of substrates, yet the understanding of how these conditions lead to ID is continuing to evolve. Some metabolic abnormalities have downstream effects including changes to DNA methylation and expression, interference with metabolic pathways such as the PI3K/AKT/mTOR pathway, and accelerated neuronal cell death as evidenced by elevated biomarkers, such as glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) [13–15].

The Mendelian disorders of the chromatin machinery (MDCMs) are a newly recognised group of genetic disorders associated with a wide range of physical and neurodevelopmental features [7,16]. The MDCMs result from variants in the genes encoding a group of proteins that are responsible for regulating chromatin structure and gene expression, by modifying histones and DNA as part of cellular processes referred to as epigenetics. The interplay between cellular metabolism and epigenetic regulation has been well described; however, how the communication between these two pathways is impacted in MDCMs is poorly understood [17,18]. Most of the early research and knowledge about the genes involved in MCDMs is derived from cancer research, but recently there has been growing awareness of the interplay between epigenetics and metabolism in the research surrounding MDCM, and increasing evidence supporting metabolic differences in MDCMs [16,19]. Learning from successful treatments used in metabolic disorders, harnessing both the metabolic environment and targeted medications, may provide opportunities for therapeutic intervention in MDCMs. An emerging consensus view is that earlier diagnosis and treatment is likely to be more effective [11,20].

2. Mendelian disorders of the chromatin machinery: what are they and how do they work?

DNA is packaged into nucleosomes by coiling around an octamer of proteins known as histones [21]. Histones are positively charged proteins and encompass five major families: H1, H2A, H2B, H3 and H4 [22]. As DNA condenses, nucleosomes form compact, elaborate structures known as chromatin [23]. Chromatin can be in an open (euchromatin) or tightly packed and condensed conformation (heterochromatin). Highly condensed chromatin reduces the ability of molecular factors to access and influence sequences that influence gene expression [19].

Conversion of chromatin to an open configuration can occur by the modification of nucleotides in the DNA or of amino acid residues in histone proteins. These modifications result in increased access of proteins and other regulatory molecules to specific areas of the genome, allowing alteration to chromatin structure and/or gene expression [19]. The modifications enable genome-associated processes to occur by providing sites that regulatory proteins or other molecules recognize: for example, transcription factors, histone chaperones, chromatin modifiers and chromatin remodellers [21]. Histones are chiefly modified on their tails, with a variety of modifications, including acetylation, other acylation, methylation, phosphorylation, ubiquitination, hydroxylation, glycation, serotonylation, glycosylation, sumoylation and ADP ribosylation [24–26].

The MDCMs affect a system of cellular machinery that include the enzymes that modify chromatin [16]. The machinery components are encoded by genes that often are dose-dependent, with the majority of MDCMs caused by heterozygous gene variant [16]. The proteins encoded by these genes may form complexes with several other protein subunits to carry out their role in chromatin modification. An example of one of these multi-subunit complexes is the MOZ/MORF complex, which comprises contributions from the histone acetyltransferases KAT6A or KAT6B, the adaptor proteins BRPF1,2 or 3, ING5 or ING4 and MEAF6 [27–29]. Pathogenic loss of function variants in the genes encoding KAT6A, KAT6B and BRPF1 are associated with genetic syndromes that cause intellectual disability [16].

It has been proposed, and in some cases shown, that in MDCMs, there are alteration in the histone modifications that determine whether chromatin is in an open or closed conformation. An open conformation is generally associated with gene expression [30]. The chromatin machinery has several functions, and chromatin associated proteins fall into four distinct categories, described as writers, erasers, readers and remodellers [30] (Fig. 1). These roles are not mutually exclusive, and writers, erasers and ~ 80% of remodeller proteins have a protein domain, termed the reader domain that is present/a key domain required for the function of reader proteins [30].

The writers are a group of proteins that function to regulate marks on histones which then can enable opening of the chromatin and increased gene expression or closing of the chromatin and gene silencing [31]. Conversely the erasers remove marks from histones, which then allows deposition of potentially opposing chromatin marks [32]. The readers are a group of proteins that sense whether the histones are marked and therefore whether the chromatin is open or closed. The readers have an important function of guiding the writers and erasers to regions of the chromatin that have specific histone modifications and in feeding this information back to the cell [30]. Remodellers of chromatin are ATP-dependent complexes that induce structural changes in chromatin through their interaction with actin and actin related domains [33,34]. Chromatin remodellers also are responsible for positioning nucleosomes so that they are able to interact with DNA which subsequently affects the transcription machinery and DNA repair [34,35].

3. Potential for metabolic treatment of the MDCMs

It is now recognised that chromatin status can be influenced by metabolic factors, and that in MDCMs these represent a potentially modifiable mechanism to alter chromatin states [19]. The chemical groups, for example acetyl- and methyl-groups, that are added to the chromatin by the writers and removed by the erasers represent a potentially modifiable substrate that may be influenced by the metabolic environment.

Some chromatin modifications, such as acetylation and methylation, may be significantly altered by changes in the intracellular environment because they have kinetic (K_m values) and thermodynamic (K_d values) properties such that the interactions are dependent on the concentration of the metabolites involved in that pathway [36]. Hence, increasing the substrate in these reactions may help to drive the processes of acetylation or methylation [19]. Identifying suitable substrates may be feasible by examining known metabolic disorders involving methylation and acetylation; however, there may also be limitations on the efficacy of substrate supplementation once the peak activity of the chromatin machinery, or enzyme, is reached. The phenotype and treatment response of the chromatin machinery, for example in Arboleda-Tham syndrome caused by heterozygous variants in the *KAT6A* gene, may depend on the location of the variants in the gene and the degree of loss of function in the chromatin machinery, necessitating a personalised approach to treatment [37].

There is also the potential for inhibition of histone substrate removal, using histone deacetylase inhibitors (HDACi) and histone demethylase inhibitors. These treatment strategies attempt to globally increase histone acetylation through preventing the removal of acetyl groups for histones, generally increasing DNA accessibility and in turn specifically influence the transcription of genes that may be involved in the

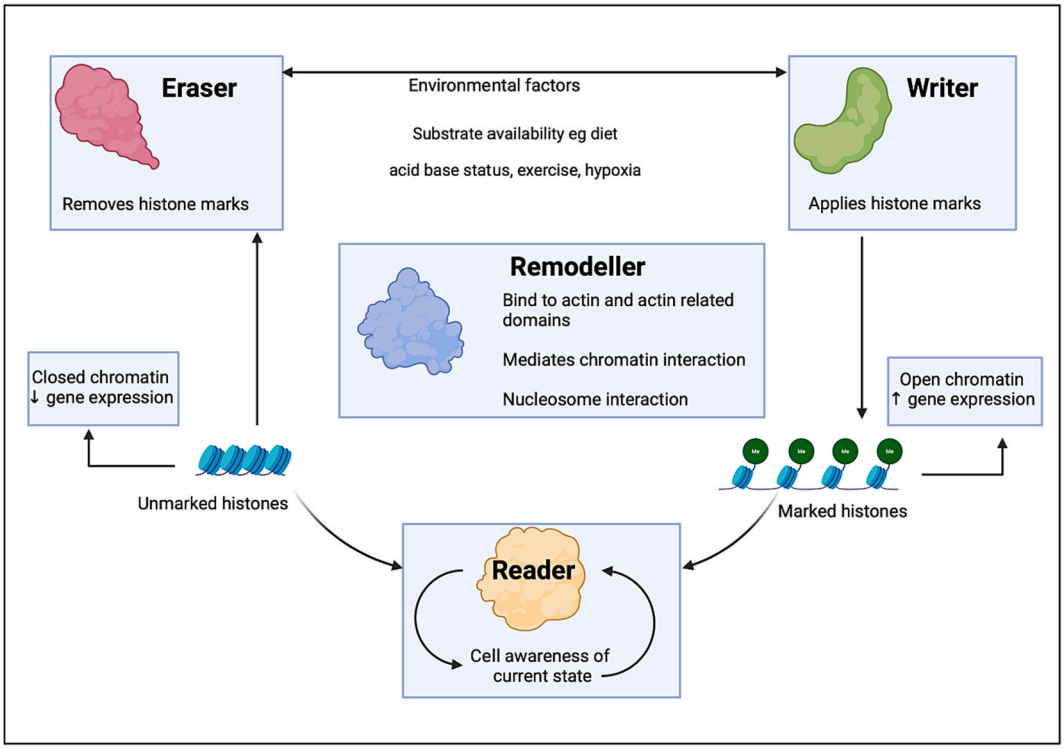

Fig. 1. Effect of the chromatin machinery on the chromatin and gene expression. The figure illustrates the relationship between the environmental and metabolic influences on chromatin writers and erasers. It also shows the effect of histone marks, depicted in green as methyl groups attached to histones, on the chromatin readers and subsequent feedback to the cell. Modified from Fahrner and Bjornsson, 2014 [19]. Figure created by biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

development of intellectual disability. For some MCDM's there have been preclinical experiments and clinical trials to test these treatment strategies, summarised in Table 1. For example Kabuki syndrome, caused by heterozygous variants in *KMT2D*, has been found to be associated with a decrease in H3K4 monomethylation and H3K27 acetylation, leading to the trial of both histone deacetylase inhibitors and histone demethylase inhibitors in mouse models, with the observation of improved behavior [38]. It is currently unknown if more targeted inhibition of the specific deacetylase and demethylase enzymes would result in better outcomes or fewer off target treatment effects.

4. Histone acetylation

Acetyl-coenzyme A (acetyl-CoA) is the donor of the acetyl-group transferred to histone lysine residues during histone acetylation. There are multiple compounds that can function as precursors for acetyl-CoA production. As depicted in Fig. 2, several discrete metabolic pathways are involved in the generation of acetyl-CoA, including protein metabolism, fatty acid metabolism, glycolysis, the tricarboxylic acid (TCA) cycle and the metabolism of ethanol. Ensuring good nutrition in MDCMs affecting histone acetylation is important to ensure an adequate supply of acetyl-CoA; ensuring that there are sufficient cofactor metabolites, such as citrate and CoA, may be important for maintaining energy production in the TCA cycle. Deficiencies in these metabolites have previously been shown to cause neurodevelopmental problems, for example, reduced citrate in neurons has been linked to early onset epileptic encephalopathy that evolves into neurodevelopmental disability [55–57].

The synthesis of intracellular CoA is a highly conserved pathway involving several enzymes that are involved in the transformation of pantothenate to CoA [58]. Pantothenate is a cofactor that is instrumental in metabolic processes involving acyl group carriage and has a carbonyl-activating group that participates in the TCA cycle and fatty acid metabolism [58]. CoA is predominantly produced in the mitochondria with homeostasis maintained by feedback inhibition [58]. The key regulatory enzyme and first initial enzyme in this process is pantothenate kinase (PANK) [58]. Subsequent to production, the CoA is then distributed in many organelles, with transporters to mitochondria and peroxisomes identified [59–61]. The conditions associated with deficient CoA production are characterised by neurodegenerative processes with neuronal brain iron accumulation and basal ganglia damage [58]. The developmental regression and basal ganglia damage observed have some clinical overlap with mitochondrial disorders, which is not surprising given that the final steps in CoA production involve a mitochondrial bifunctional enzyme (COASY) [58]. Analysis of fibroblast cells and plasma from patients with pantothenate-kinase associated neurodegeneration (PANK) have demonstrated abnormal cholesterol and lipid biosynthesis, with the fibroblasts also demonstrating mitochondrial dysfunction [62,63].

An example of a potentially treatable MDCM in which histone acetylation is compromised is the autosomal dominant disorder Arboleda-Tham syndrome (MIM616268), caused by heterozygous loss of function variants in *KAT6A* leading to syndromic intellectual disability and complex speech and language disorders [64,65]. Associated features include microcephaly, cardiac abnormalities, hypotonia, feeding difficulties, constipation, and frequent infections [64]. In *KAT6A* patient derived fibroblast models from several patients with *KAT6A*, supplementation with L-carnitine and pantothenate (B5) has been reported to rescue histone acetylation, partially correct protein and transcriptomic levels and improve cell biogenics; however, a limitation of this study is that the baseline metabolomic fingerprint of *KAT6A* is not known, so it is unknown if there are other metabolic substrates that may benefit from supplementation [39]. Understanding of *KAT6A* biology has evolved from cancer research, where its inhibition induces cellular senescence through the INK4/ARF pathway and also through down-regulation of the PI3K/AKT pathway [66,67]. The PI3K/AKT/mTOR

Table 1
Examples of Mendelian Disorders of Chromatin Machinery, metabolic pathways affected and results from preclinical and human research using substrate modification of histones via supplementation or inhibition of removal of substrates.

Gene	Chromatin interaction	Primary metabolic pathway affected	Cellular/Animal research	Human research
KAT6A	Writer/ Reader	Histone acetylation	• Substrate supplementation of carnitine and pantothenate in patient derived fibroblasts demonstrated improvement in histone acetylation with partial correction of protein and transcriptomic changes [39].	• No current clinical trials
KAT6B	Writer/ Reader	Histone acetylation	• No published trials	• No current clinical trials
BRPF1	Reader	Histone acetylation	• No published trials	• No current clinical trials
KMT2D	Eraser	Histone methylation	• Mouse model demonstrated improved cognition and neurogenesis with ketogenic diet and administration of beta-hydroxybutyrate [40]. • Mouse model demonstrated improved DNA methylation with HDACi AR-42 [41]. • Mouse model demonstrated improvement of neurogenesis and normalisation of hippocampal memory deficits with treatment with HDACi – AR-42 (42). • Mouse model demonstrated normalisation of hippocampal memory deficits with administration of lysine-specific demethylase 1 A (KMD1A) inhibitor TAK-418 (43).	• No current clinical trials
CREBBP	Writer/ Reader	Histone acetylation	• Patient derived iPSC neurons demonstrated evidence of rescue of function with HDACi Trichostatin A and valproic acid [44]	• Unpublished trial: Rubinstein-Taybi syndrome: Functional Imaging and Therapeutic Trial (RUBIVAL), ClinicalTrials.gov ID NCT01619644.
MECP2	Reader		• Triheptanoin treatment in male Mecp2 knock out mouse improved longevity, motor function and social interaction [45]. • Acetyl-L-carnitine supplementation in Mecp2(1lox) null mice resulted in improvement in hippocampal dendritic morphology abnormalities and early in life resulted in improvements to motor and cognitive functions early in life, but this was not sustained as the mice aged [46]. • Treatment with selective HDAC6 inhibitor tubastatin A restores microtubule dynamics in astrocytes and reversed early impaired exploratory behavior deficits in Mecp2$^{308/y}$ mouse model of Rett syndrome [47]. • Treatment with Valproate or KW-2449, a multikinase inhibitor, resulted in improvements in neuronal deficits and evidence of restoration towards normal transcriptome changes in cerebral organoids derived from human embryonal stem cells [48].	• Ketogenic diet trialled patients with a reduction in seizure frequency [49,50]. • Creatine supplementation in a double blind randomised trial demonstrated increases in global methylation, but no statistically significant difference on clinical scoring symptoms [51]. • Folinic acid trialled in a small number of patients normalised 5-MHTF and 5-HIAA levels and resulted in partial clinical improvement [52]. • Folinic acid trialled as a treatment in patients with Rett syndrome for 6 months with low CSF folate levels did not result in clinical improvement [53]. • Folinic acid supplementation in randomised blinded cross over trial improved 5-MTHF levels but did not result in improved clinical outcome measures [54].

pathway is also becoming more prominent in intellectual disability research, with downregulation and upregulation in mTOR implicated in the biology of intellectual disability [68]. It is important to characterise the metabolomic fingerprint and biomarker characteristics of *KAT6A* and other MDCMs to better understand the metabolic processes contributing to the ID in these conditions and to observe if biochemical and biomarker correction may be possible in model systems and humans.

5. Histone methylation

Histone methylation influences gene expression by the application of methyl groups to histones. The appropriate expression of genes that provide instructions for neurogenesis and neural migration is important for the development of normal neural networks and when this process is dysregulated from abnormal gene expression then there can be adverse cognitive outcomes [69,70]. An example of histone methylation influencing neurodevelopment is the methylation of Histone H3 Lysine K4 (H3K4), which is important for learning and memory. MCDM's involved in methyltransferase activity and demethylase activity cause a range of ID syndromes including Kleefstra syndrome and Kabuki syndrome [71]. As with histone acetylation, identifying potential therapeutic targets for supplementation in the methylation cycle (Fig. 3), involving cobalamin, folate, betaine and methionine, to increase the pool of methyl-group donors may become important to drive methylation [72]. Genetic conditions affecting B12 metabolism, folate metabolism and methylenetetrahydrofolate reductase (MTHFR) are well established to cause neurodevelopmental regression, poor growth and microcephaly [73,74]. Conversely, abnormalities in these pathways leading to elevations of homocysteine lead to overgrowth [75]. These are interesting observations given that many of the MDCMs demonstrate abnormal growth outcomes, with small stature and overgrowth being reported features [16].

Disorders involving folate metabolism cycle, such as severe MTHFR deficiency and severe folate deficiency (caused by inadequate cellular uptake of folate when the folate receptor alpha (FOLR1) is dysregulated), lead to a deficiency of components of the methylation cycle, and manifest with early seizure disorders, failure to thrive, microcephaly and intellectual disability [76]. These metabolic disorders involving folate metabolism have some clinical overlap with Rett syndrome, an MDCM caused by pathogenic variants in the gene encoding methyl-CpG-binding protein 2 (*MECP2*). Folate levels in cerebrospinal fluid have been found to be reduced in patients with Rett syndrome and treatment with folinic acid has been trialled for one year in females with Rett syndrome aged 2–30 years [54]. Although this treatment did not result in clinical benefit or change in the levels of CSF folate metabolites the study, it is possible that treatment might be successful if commenced earlier, continued for longer, or combined with other therapies, such as histone demethylase inhibitors [53,54,77]. The other possibility to consider in early trials prior to clear genetic diagnosis, for example in patients with a clinical diagnosis of Rett syndrome, but no causative MECP2 variant, there may have been a variety of genetic conditions

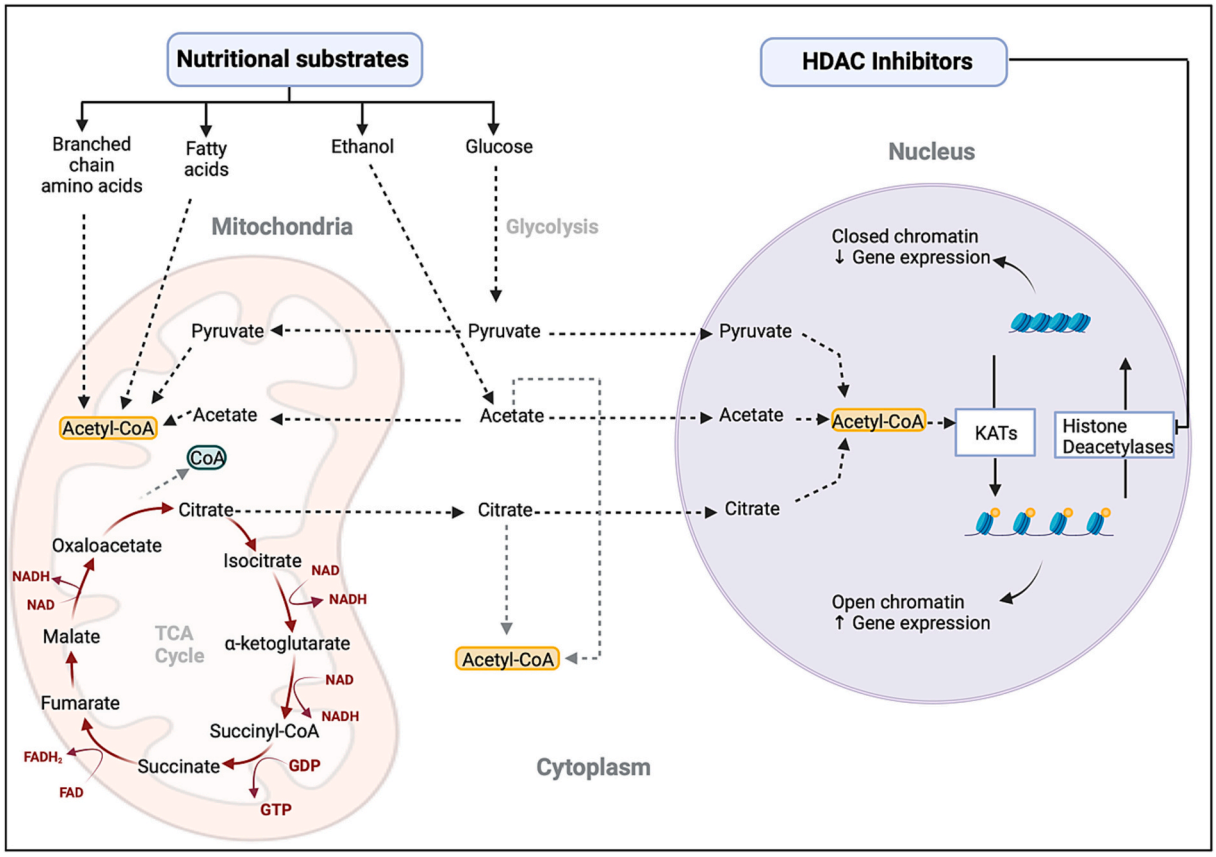

Fig. 2. Effect of nutritional substrates on the acetyl-group donor, acetyl-CoA, and effects on histone acetylation. This figure demonstrates the metabolism of Acetyl-CoA and potentially modifiable pathways for treatment to increase metabolic precursors of Acetyl-CoA and the potential impact of treatment with histone deacetylase inhibitors. Figure legend Acetyl-CoA; acetyl-coenzyme A, CoA; coenzymeA, NAD; nicotinamide adenine dinucleotide, NADH; reduced for of NAD with hydrogen, GDP; Guanosine diphosphate, GTP; Guanosine triphosphate, FAD; flavin adenine dinucleotide, FADH; reduced form of flavin adenine dinucleotide with hydrogen, KATs; lysine acetyltransferases, HDACi; histone deacetylase inhibitors. Modified from Sheikh et al. [18]. Figure created by biorender.com.

causing their clinical phenotype, resulting in varying degrees of responsiveness to treatment. Other disease specific biomarkers, such as CSF lipidomics analyses, might be an effective tool to measure response to treatment in MECP2 disorders because treatment might alter cholesterol biosynthesis in the brain but not plasma [78].

In contrast, some of the disorders of the methylation cycle, such as homocystinuria due to cystathionine beta-synthase (CBS) deficiency, lead to significant elevations of plasma homocysteine levels and cause ID and overgrowth [75]. In double knock out mouse models of homocystinuria due to CBS deficiency, increased methylation of H4K20me1 and increased gene expression of histone demethylase PHF8 was reported [13]. The same study also reported increased mTOR expression, autophagy downregulation and increased expression of biomarkers that indicate neuronal damage, such as neurofilament light chain and glial fibrillary acidic protein [13]. Abnormal homocysteine levels and abnormal DNA methylation have also been reported in neurodegenerative conditions, such as Alzheimer's disease [79]. The development of biomarkers for Alzheimer's disease, such as neurofilament light chain, may also have clinical utility in the MDCMs for disease monitoring and assessing response to treatment [80,81].

6. Limitations of substrate supplementation

One potential issue with substrate supplementation is that there may be a narrow therapeutic window where patients may experience a clinical benefit. For some substrate treatments, the doses used for tolerability of supplements might be derived from treatment in other diseases involving metabolism. For some substrates, such as carnitine, this may be limited by gastrointestinal tolerability or tolerability of other side effects, such as the production of trimethylamine causing a fishy odour. For other substrates, such as treatment of the methylation cycle, it is important to recognize that methylation of different chromatin targets results in different transcriptional outcomes. Trimethylation of histone H3 lysine 4 is associated with active gene transcription, whereas trimethylation of histone H3 lysine 27 is associated with gene repression [82,83]. Therefore, simply raising or lowering general methylation levels may not achieve the desired therapeutic result.

It is also essential to anticipate and treat deficiencies that occur because of modulating the methylation cycle. One of the best examples of this is the treatment of homocystinuria with betaine and the need for surveillance of vitamin B12 and folate, which decrease over time as they are consumed in the methylation cycle [75,84]. Studying neuronal models of conditions, for example by the use of metabolomic profiling, could identify biomarkers that will be useful in vivo to monitor and optimise supplementation.

7. Potential treatments with disease modifying drugs

Histone deacetylase inhibitors (HDACi) and lysine-specific demethylase 1 inhibitors (KDM1Ai) inhibit histone deacetylation and histone demethylation processes, respectively, and may be therapeutic strategies in the treatment of certain MDCMs [85–87]. There are several classes of HDACi based on their chemical structure (outlined in Table 2) [32]. The lysine-specific demethylase 1 inhibitors have actions that can be irreversible or reversible, some of these compounds are also summarised in Table 2 [88]. This includes the zinc dependent group of

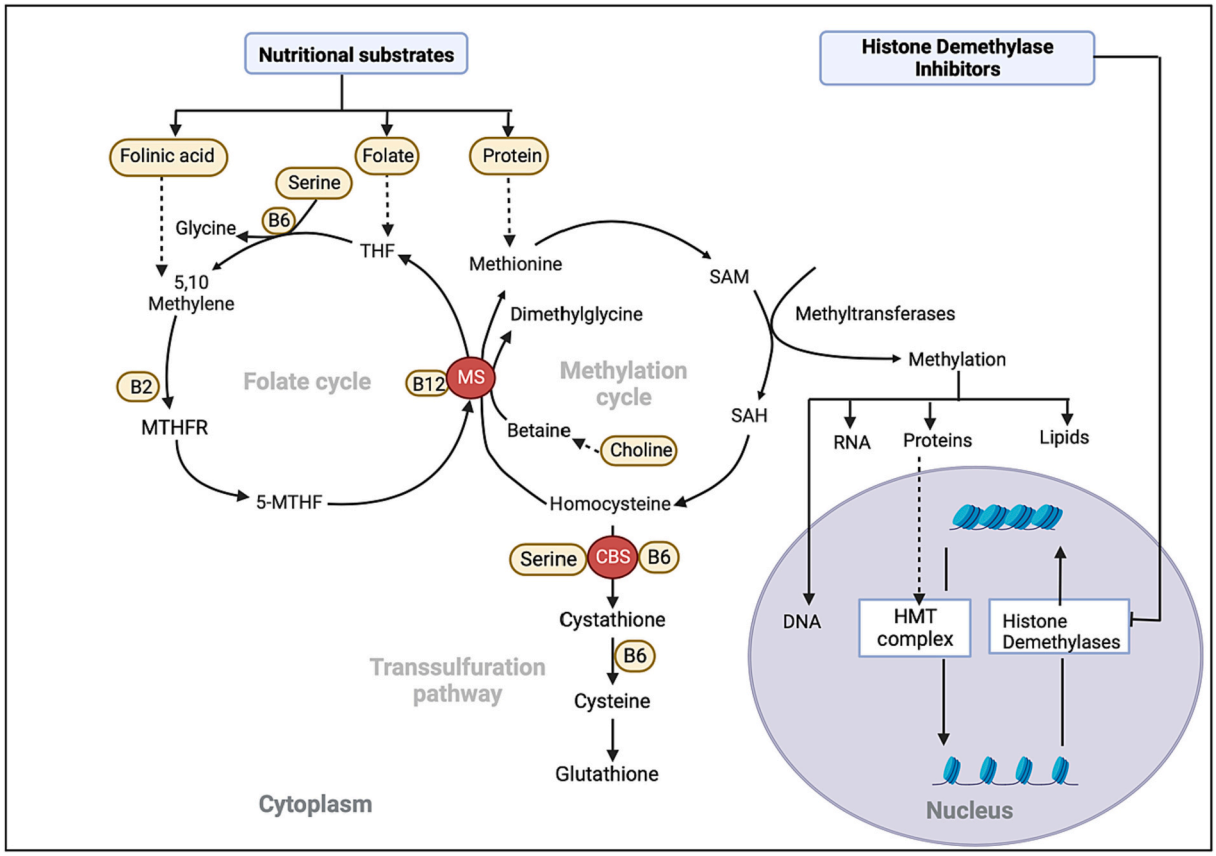

Fig. 3. Effect of nutritional substrates on precursors for methylation and effects on DNA and histone methylation. This figure demonstrates the metabolic pathways that influence the methyl group precursors. Methylation is influenced by several metabolic pathways including the folate cycle, methylation cycle and transsulfuration pathway. Figure legend B6; pyridoxine, B2; thiamine, THF; tetrahydrofolate, MTHFR; methylene tetrahydrofolate reductase, MS; methionine synthase, SAM; s-adenosylmethionine, SAH; S-Adenosyl-L-homocysteine. Drawn based on Dai [19] and Morris et al. [75]. Figure created by biorender.com.

Table 2
Classes of Histone Deacetylase Inhibitors and Histone Demethylases.

Class of inhibitor	Example of inhibitor	
Class A HDACi	Trichostatin A (TSA)	SAHA (Voronistat/
Hydroxamic acids	LBH589 (Panobinostat)	Zolinza)
	PDX101 (Belinostat)	SB939 (Pracinostat)
Class B HDACi	Valproic acid	AN-9 (Pivanex)
Short chain fatty acids	Butyric acid	
Class C HDACi	CI-994	MGCD0103
Benzamides	M344	(Mocetinostat)
		MS-275 (SNDX-275/
		Entiostat)
Class D HDACi	Apicidin	Largozole
Cyclic Peptides	CHAP31	Trapoxin (TPX)
	FK228 (Romidepsin/	
	Istodax)	
Irreversible lysine	TCP	Compound 15
demethylase 1 inhibitors	S2101	Pargyline
	Compound 4c	Bizine
	ORY1001	Compound 5a
	Compound 11 h, RN1	Compound 3
	Compound 1c	Compound 1a
	Compound 191	Compound 1
	OG-L002	Compound 18
	GSK2879522	
Reversible lysine demethylase	Compound 6d	Compound 6b
1 inhibitors	Cryptotanshinone	Compound 17
	Compound 26	NCL-1
	Verlyndamycin	N-alkyl NCL-1
	Compound 9a	Namaline
	Curcumin	PRSFLV SNAIL Peptide
	HCI-2509	CBB107
	Compound 5n	Compound 16q

histone deacetylase inhibitors and the inhibitors of the sirtuin (SIRT) group of histone deacetylase, which are dependent on nicotinamide-adenine-dinucleotide (NAD) [89]. Some of these drugs (or compounds) have already been trialled in mouse models and humans for other conditions related to cancer, neurodegeneration or neurological deterioration [86,90].

HDAC inhibitors have been used to treat animal models of neurocognitive diseases, with improved learning and neuroprotection demonstrated in mouse models for Rubinstein-Taybi syndrome, Huntington disease, Alzheimer's disease, Parkinson's disease and spinal muscular atrophy [91–103]. Similar improvement in clinical phenotype was reported using HDAC inhibition of *Drosophila* models of Huntington disease and Parkinson's disease [104,105]. Increased expression of the survival of motor neuron 2, centromeric (*SMN2*) transcript and elevated steady-state SMN2 were observed in patient derived fibroblasts cells from patients with Spinal Muscular Atrophy after treatment with benzamide M344 and LBH589 [106,107]. Some of these findings have been translated to clinical trials in frontotemporal dementia, Alzheimer's disease, Huntington disease, Parkinson's disease [85,108].

The use of HDAC inhibition has been trialled as a potential treatment strategy in neuronal stem cell models and animal models of some MCDM. HDAC inhibition using trichostatin A was recently trialled in iPSC-derived neurons from patients with Rubinstein-Taybi syndrome, which is caused by pathogenic variants in the gene encoding cyclic adenosine monophosphate response element binding protein binding protein (*CREBBP*) [44]. Cortical neurons treated with trichostatin A, both short-term (1 week) and long-term (6 weeks), demonstrated complete/partial rescue of key molecular disease-associated phenotypes such as nuclear area, neuronal excitability and sodium/potassium

channel activity [44]. Similar findings of rescue of nuclear size were demonstrated with valproic acid treatment [44]. However, a limitation of these studies is that both trichostatin A and sodium valproate have the potential for off-target effects as a result of non-selective HDAC inhibition. There are also no disease specific biomarkers currently available to measure treatment effect in vivo. Valproic acid supplementation has also been trialled in MECP2 in human embryonic derived knock out cerebral organoids, which had demonstrated downregulation of the genes involved in the PI3K/AKT pathway in untreated form [48]. Treatment of these organoids from day 10 with valproic acid demonstrated restoration of the genes in this PI3K/AKT pathway [48].

Histone demethylase inhibitors, targeting lysine-specific demethylase 1 A, which is responsible for removing H3K4 methyl marks, have recently been shown to improve the dysregulated gene expression and hippocampal memory defects in mice models of Kabuki syndrome, caused by pathogenic variants in the gene encoding the lysine-specific methyltransferase 2D (*KMT2D)* [42,43].

8. Potential complications with using disease modifying drugs

The use of HDACi and histone demethylase inhibitors is not without potential complications as these treatments do not target specific histone modifications and, in addition, may have off target effects. For an example of this sodium valproate demonstrates off target effects which increase histone acetylation and DNA demethylation [109]. Fetal exposure to sodium valproate during gestation has been reported to result in a teratogenic effect in both animal models and humans, with dysmorphic facial features, congenital malformations, skeletal abnormalities and neural tube defects reported [110]. The problems associated with sodium valproate administration are not limited to the physical malformations, with neurodevelopmental issues including reduced intellectual functioning and autistic traits also reported [111,112]. The changes induced by valproate exposure include histone acetylation and DNA methylation, and chromatin remodelling genes have also been reported to be differentially expressed subsequent to valproic acid exposure [113].

Treatment with sodium valproate can also cause hepatotoxicity and manifest with hyperammonaemic encephalopathy [114]. Valproate is metabolised in the liver via several processes including oxidation in the cytosol and mitochondria and glucuronic acid conjugation [114]. Valproate decreases carnitine synthesis by decreasing the precursor concentration of alpha-ketoglutarate [114].

In addition to the off target effects, treatment with HDACi may have a narrow therapeutic window. Currently there aren't any robust biomarkers to monitor off target effects in HDACi, which makes the development of robust biomarkers important to minimise harm from treatment.

9. Potential treatments: the path forward

The outcomes of substrate manipulation and modulation of histone modification by inhibitors of deacetylation and demethylation in mouse and patient-derived neural stem cells demonstrates the potential of these treatments for treating MDCMs in vivo. Characterising the specific metabolomic profile of MDCM patients may provide opportunities for targeted intervention with supplementation of deficient metabolites and potentially therapies to enable the reduction of toxic metabolites.

Currently there is a knowledge gap in many of the MDCMs where the metabolomic profile of the disorders is unknown. Characterising the metabolomic profile prior to the use of potential therapeutic treatments would be helpful to understand the pathophysiology of the MDCMs, to identify potential metabolic supplements and to evaluate the impact of treatments. There is also a need for the identification of non-invasive biomarkers that may be used to monitor treatment response.

The development of biomarkers is particularly important as many children will have significant ID that will impact on their ability to communicate, complete developmental assessments and track progress from interventions. These biomarkers used in conjunction with substrate supplementation and using HDAC inhibitors and histone demethylase inhibitors represent an additional therapeutic opportunity. Some of these drugs that modify chromatin marks have previously been trialled or are in clinical use in cancer, epilepsy and neurodegenerative disorders. The expansion of these drugs to treatment of some of the MDCMs presents a therapeutic opportunity to specifically targeted treatments.

Understanding the disordered metabolic pathways that occur as a result of MDCMs may provide other potential treatment strategies if substrate modification is not successful in restoring neurometabolism. The PI3K/ATK/mTOR pathway is an obvious candidate for targeted treatment as this has been modulated in-vitro in other disorders causing intellectual disability.

10. Conclusions

The MDCMs are a potentially treatable cause of intellectual disability, particularly those that may be amenable to supplementation of precursor chemicals to supplement deficient metabolites that are utilised by chromatin writers to modify histones. The use of medications that prevent the removal of histone modifications may also provide a therapeutic strategy to treat these conditions. As the children with many of these conditions may have significant neurodevelopmental disability, the identification of disease biomarkers may provide important tools in advancing our knowledge and understanding of these conditions. Substrate manipulation and the use of drugs to modify chromatin marks have some therapeutic limitations and potential off-target effects. The development of disease biomarkers will become important for monitoring treatment success and to enable determining the optimum doses of substrate and medications.

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CRediT authorship contribution statement

Sarah Donoghue: Conceptualization, Writing – original draft, Writing – review & editing. **Jordan Wright:** Writing – original draft, Writing – review & editing. **Anne K. Voss:** Writing – original draft, Writing – review & editing. **Paul J. Lockhart:** Writing – original draft, Writing – review & editing. **David J. Amor:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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