**Editorial: Molecular Metabolism Special Issue ‘Epigenetics and Metabolism’**

**You are what you eat - how nutrition and metabolism shape the genome through epigenetics**

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**Highlights**

- The epigenetic machinery depends on the cellular metabolism

- Epigenetic enzymes and chromatin can act as metabolic sensors

- The information flow between metabolism and chromatin is bidirectional

- Physiology and metabolism shape epigenetic mechanisms

- The links between epigenetics and metabolism have major implications for human health

**Keywords:** metabolism, epigenetics, chromatin, physiology**Abstract**

Cellular metabolism and “epigenetic” gene regulation are closely inter-connected. As diet and nutrition impact on epigenetic processes through metabolic intermediates and as many epigenetically transmitted traits are linked to metabolic diseases the cross-talk between metabolism and epigenetics has major implications for human health. In this special issue ‘Epigenetics and Metabolism’ of *Molecular Metabolism* we have brought together a collection of excellent review articles from experts in the field that highlight important recent scientific developments and discuss a number of key concepts to illuminate the links between epigenetic gene regulation and metabolism from various angles. Here we will present a synopsis of how nutrition and metabolism can shape the output from the genome through epigenetic pathways.We want to provide readers with a broad overview of how chromatin and metabolism are inter-connected and the implications if this crosstalk goes wrong. We hope to create a reference in order to stimulate discussions and drive research in the field further.

**1. Introduction**

One of the hallmarks of all living beings is their ability to extract energy from their surroundings and use it in a process termed metabolism to grow and reproduce. During evolution life had to “learn” how to cope with changing environments and to exploit even limited and unstable sources of energy. The ability to take up and process energy from diverse sources, and to adjust their metabolism to the availability of nutrients is therefore fundamentally engrained in the nature of all living things. This holds true for single-celled microorganisms that need to survive in competitive environments as well as for multicellular organisms such as plants and animals whose cells need to function within the context of tissues. With increasing complexity organisms have evolved more and more intricate networks of enzymes and co-factors that interconvert metabolites in order to satisfy their need for energy and to provide chemical building blocks.

The biochemical reactions that take place in the cells are based on the versatility of carbon chemistry. The carbon source is therefore at the centre of an organism’s metabolism and determines the modes of energy and biomass production. Being able to produce their own energy and building materials autotrophic organisms have often evolved to be immobile or incapable of active migration. Since these organisms cannot simply “run away” they have to cope with their immediate surroundings and they need to be able to withstand fluctuations in e.g. light, temperature, and water availability, and to adapt to the conditions in their habitat. For autotrophic organisms adaption of their metabolism to the environment is therefore of major importance. Heterotrophic organisms, on the other hand, have evolved means to sense nutrients, and they have adaptions that allow them to get to, capture, and digest food stuffs. Their metabolic circuitries have evolved to be able to deal with different types and changing amounts of food.

The information for how, when, and where to make the enzymes that are required for adenosine triphosphate (ATP) production and the synthesis of biomolecules is encoded in an organism’s genome. All living beings must be able to dynamically change the gene expression programmes of their cells so that they can adjust their metabolism according to the availability of different carbon sources and other essential nutrients. This metabolic response can be fast, if there is a need for a rapid adjustment to an external stimulus, or slow, if long-term adaption to a persistent condition is required. It might be advantageous for an organism to build a memory of the response to a certain stimulus, or even pass this memory on to subsequent generations, so that if the stimulus reoccurs subsequent responses can be faster or stronger, or offspring is already primed for persistent environmental conditions.

As the genetic information of an organism encoded in the DNA sequence is generally fixed and cannot be quickly changed in response to an external stimulus it is the output from the genome, i.e. the expression of genes, that is regulated. Rapid responses are typically mediated by pre-existing sensors, signaling molecules, and transcription factors that trigger a transcriptional response. Such relatively simple responses, which are typical for prokaryotic microorganisms, are more or less direct and usually transient. Once the stimulus is gone the response typically fades away. Eukaryotic organisms stow away their genomes in the nucleus, where it is packaged in the form of chromatin, a nucleoprotein complex composed of the DNA and histones, and other structural and regulatory proteins. This packaging of the genetic material adds an additional layer for regulating the output from the genome through “epigenetic” mechanisms that allow cells and organisms to store and transmit hereditary information without changing their DNA sequence. The epigenetic machinery consists of enzymes that deposit covalent chemical modifications on the DNA and on histones (so-called writers) or that remove them (erasers), proteins that can recognise such modifications and thereby read out epigenetic information (readers), and chromatin remodeling enzymes that can load, evict, or shift histones on the DNA or exchange canonical histones against specialised histone variants [1-3]. Epigenetic mechanisms regulate all chromatin-templated processes including gene expression, DNA replication, and DNA Repair. Due to their stimulating or repressing functions in gene transcription histone modifications and DNA methylation can reinforce and perpetuate transcriptional programmes. In addition to short-term transcriptional circuits, these chromatin-based mechanisms enable eukaryotic cells to form a stable more long-term epigenetic memory. The reversible nature of the storage of epigenetic information in chromatin enables cells and organisms to respond and adapt to external stimuli, and to inscribe information about the environment into their epigenomes, opening up the possibility to pass on heritable information to their offspring in a non-mendelian fashion. Increasingly, the importance of non-coding RNAs and RNA modifications is recognised as an additional mechanism for the transgenerational inheritance of epigenetic information [4].

Over recent years the profound entanglement between cellular metabolism and epigenetic regulation has increasingly been appreciated. However, we are only starting to understand how diet and nutrition impact on human health through epigenetic processes, and the role that metabolism plays in various diseases via epigenetic gene regulation and inheritance. In this special issue ‘Epigenetics and Metabolism’ of *Molecular Metabolism* we have assembled a collection of review and opinion articles that highlight important recent developments in our knowledge of how chromatin and metabolism are linked. We are delighted that we were able to put together such an interesting line up of articles that will give the readers a broad overview over the links between epigenetic gene regulation and metabolism from various angles, and we are deeply grateful to all the authors for their contributions. In this editorial we will discuss a number of key concepts that connect these reviews. We will only include a small number of citations and we apologise to all colleagues whose work we are not citing directly here. References to their original work can be found in the individual review articles which we will refer to in the text.

**2. The Epigenetic Machinery Depends on the Cellular Metabolism**

One of the main aspects to be considered when looking at the interplay between metabolism and epigenetic processes is that chromatin modifying enzymes utilise co-factors derived from central metabolic networks [5,6]. For example, acetyl co-enzyme A (acetyl-CoA) is used by histone acetyl-transferases (HATs) for the acetylation of histones. The universal methyl donor S-adenosyl-L-methionine (SAM) is a co-substrate for lysine methyltransferases (KMTs) and DNA methyl transferases (DNMTs) to methylate histones and DNA, respectively. Chromatin remodeling enzymes require the energy from ATP. In addition, chromatin modifying and de-modifying enzymes also require other small molecule co-factors that are key metabolites in the cell. For example, alpha-ketoglutarate (-KG) is a co-substrate for jumonji lysine demethylases (Jmj-KDMs) and TET enzymes, flavin adenine dinucleotide (FAD) is an essential co-factor for the lysine de-methylases LSD1 and LSD2, and nicotinamide adenine dinucleotide (NAD+) is required by PARP1for ADP-ribosylating proteins in chromatin. The biosynthesis of these co-factors depends on vitamins, essential amino acids, and other trace elements that need to be taken up from the environment. Interestingly, the central cellular metabolism also produces inhibitors of epigenetic enzymes, for example succinate and fumarate are inhibitors of Jmj-KDM and TET enzymes, and S-adenosyl-L-homocysteine (SAH), the product of methylation reactions utilising SAM, is a potent KMT inhibitor. These examples illustrate that the epigenetic machinery directly depends on many core metabolic intermediates and that epigenetic processes and chromatin regulation must always be considered in the wider context of the cellular metabolism (Figure 1). This is a central theme that in one way or other forms the basis of almost all reviews in this special issue ‘Epigenetics and Metabolism’.

**3. Compartmentalisation of Metabolic Processes**

A second important aspect that characterises cellular metabolism is the localisation of metabolic enzymes to different cellular compartments, e.g. to the cytosol, the nucleus, or mitochondria. With respect to epigenetic regulation this means that co-factors of epigenetic enzymes exist in different subcellular pools and that their availability can be regulated. By targeting metabolic enzymes to chromatin co-factors can be produced in specific subnuclear locations and could form metabolic micro environments. This could enable gene locus-specific activation of e.g. modifying or de-modifying enzymes. In support of this are findings that some epigenetic modifiers interact with metabolic enzymes [7].

It turns out that the mitochondria are of central importance for epigenetic processes as they harbour many metabolic reactions that provide key metabolites required for epigenetic enzymes (Figure 1). The mitochondrial matrix is the principle site of the tricarboxylic acid (TCA) cycle and thus a major control point for the redox state of a cell that determines the availability of NAD+ and FAD. Under aerobic conditions oxidative phosphorylation (OXPHOS) in the inner mitochondrial membrane produces most of the ATP of eukaryotic cells, which is used by chromatin remodelers. Finally, mitochondria are the sites of beta-oxidation (-ox) and provide the majority of acetyl-CoA and other acyl-CoA’s (see below). The cross-talk between mitochondria and the nucleus is discussed in detail in the review by Bannister and colleagues **[8]**.

**4. Epigenetic Enzymes and Chromatin Act as Metabolic Sensors**

The tight coupling of epigenetic processes to the cellular metabolism via the availability of co-factors also means that the epigenome and thereby the gene expression programmes of cells and organisms respond to metabolic changes and perturbations. SAM, acetyl-CoA, NAD+, and FAD levels can be regarded as metabolic biosensors for the energy status of a cell with epigenetic enzymes acting as funnels that orchestrate the response of chromatin to the metabolic state [9].

Histones can be modified by various types of acylation [10]. For this a number of HATs can use acyl-CoAs other than acetyl-CoA as co-factors. These acyl-CoAs are derived from different nutrient sources through multiple distinct metabolic processes including lipid metabolism, ketone body metabolism, and amino acid catabolism, but they can also stem from short chain fatty acids produced by the intestinal microbiota in the gut (see below). As each acyl-CoA species has distinct roles in metabolism and their corresponding histone acylations have different functional roles in gene regulation they can signal information about the predominant nutrient and energy source and the metabolic pathways to chromatin. Histone acylations can thereby act as genomic sensors for the metabolic status of the cell. Different histone acylations and how they connect metabolism with chromatin regulation is discussed in the review by Wellen and colleagues **[11]**.

Similar to histone acylations ATP-dependent chromatin remodelers like the INO80 and SWI/SNF (BAF) complexes regulate the expression of genes that are required for energy metabolism pathways in response to changes in nutrient availability. Their primary function is to reposition nucleosomes at the promoters of target genes to regulate their accessibility to transcription factors. In fact, chromatin remodelers were first identified in the yeast *S. cerevisiae* as transcriptional regulators of genes that mediate growth on different carbon sources, such as glucose, sucrose or inositol (SWI/SNF – switch/sucrose non-fermenting; INO – inositol metabolism). For example, in yeast INO80 and SWI/SNF regulate the switch between respiration and fermentation. In mammals INO80 acts to keep cell division in check when excess nutrients are available, and BAF regulates tissue-specific glycolytic metabolism. This function of chromatin remodelers in metabolic sensing is discussed in the review by Morrison **[12]**.

While histone acylations and chromatin remodeling are dynamic and enable cells to quickly respond to shifts in the availability and type of carbon source, the genome can also build up an “epigenetic” memory of nutritional conditions that persists for extended periods. Here the main driver is stable methylation of the DNA by DNMTs and the key metabolite is SAM. SAM production requires ATP (that it turn depends on the availability of a carbon source), methionine, folate (vitamin B9), betaine, and cobalamin (vitamin B12). Humans have to take up methionine and the vitamins with the diet. Long-term, but even short but drastic, imbalances or undersupply of an energy source, methionine and vitamins (i.e. malnutrition) can have effects on global and gene-specific DNA methylation levels (and also histone methylation), which can induce long-lasting changes in gene expression patterns that might affect an individual’s health, and that might also be passed on to the offspring. These topics are central themes of the reviews by Rando and colleagues **[13]** and by Grundberg and colleagues **[14]**. These phenomena are even more pronounced in plants where non-CG methylation is reversible and highly sensitive to changes in folate levels creating stable epi-alleles that can be passed on to subsequent generations (see below).

**5. The Information Flow Between Metabolism and Chromatin is Bidirectional**

The deep entanglement between metabolism and epigenetic gene regulation also means that the epigenetic machinery can affect metabolism itself. As described above, the responses to metabolic signals funneled onto chromatin through acyl-CoAs **[11]** and chromatin remodelers **[12]** lead to switches in transcriptional programmes that change the complement of metabolic enzymes. The epigenetic enzymes thereby bring about a remodeling of metabolic networks, creating a feedback loop. Another example for the cross-talk between metabolism and chromatin is the division of the genetic material in eukaryotic cells into the nuclear and mitochondrial genomes. Since the genetic information for the vast majority of mitochondrial proteins is encoded in the nuclear genome their expression is controlled by chromatin-based regulatory mechanisms. Therefore, mitochondria cannot exist without intact chromatin while chromatin cannot be regulated properly without mitochondria (see above) creating a mutual interdependency **[8]**.

 But the epigenetic machinery can affect the cellular metabolism even more directly. The enzyme PARP1 (Poly [ADP-ribose] polymerase 1) that has multiple functions in e.g. gene transcription and DNA damage repair requires NAD+ for ADP-ribosylating target proteins which directly affects chromatin structure and activity. But PARP1 is also a main consumer of NAD+ and can significantly diminish the cellular NAD+ pool, thereby affecting redox and ATP metabolism in the cytosol and mitochondria [15]. In muscle cells PARP1 is directly regulated by the histone variant macroH2A1.1 that binds to auto-PARylated PARP1 via its macro-domain and inhibits its enzymatic activity. Thus chromatin is not only a passive “consumer” of metabolic products but can actively control the redox metabolism and thereby affect OXPHOS and ATP production in the mitochondria. This intriguing role of PARP1 and macroH2A1.1 in metabolism and how it affects human health is the focus of the review by Buschbeck and Ladurner and colleagues **[16]**.

**6. Physiology and Metabolism Shape How Organisms Adapt Epigenetic Mechanisms to their Environment**

A further interesting aspect from the evolutionary perspective is how distinct metabolic programmes result in specific adaptions of the epigenetic machinery. The guts (or digestive systems) of multicellular heterotrophic organisms, such as animals, are populated by enormous amounts of microorganisms that help the host to digest food and that have co-evolved with the host over very long time scales. In addition to direct effects of metabolites taken up from the diet the food that passes through the gut is broken down and processed by these microorganisms. Thus, there is an interaction between the host and its microbiota that is mediated through molecules and metabolites secreted by the gut microbes. Gut bacteria synthesise, for example, the vitamins cobalamin (vitamin B12), riboflavin (vitamin B2), and folate (vitamin B9) that are required for the synthesis of co-factors (see above), and they secrete short chain fatty acids (SCFAs) that can be potent competitive histone deacetylase (HDACs) inhibitors. This inhibition of HDACs is a major determinant in the microbiome-host interaction. SCFAs are also transported across apical membranes of gut epithelial cells, and converted to SCFA-CoAs to serve as substrates for acyl-transferases. These metabolites influence gene regulation in the host by shaping the epigenome, predominantly of cells in the gut epithelium. In addition to affecting the host’s immune system this has significant consequences for overall metabolic health and cancer defense. Aspects of the host-microbiome interactions and the effects of SCFAs on the epigenome are discussed in the reviews by Varga-Weisz and colleagues **[17]** and by Wellen and colleagues **[11]**.

The situation is different in autotrophic organisms such as plants. Here, the availability of light (i.e. the day/night cycle) and their immobile lifestyle are dominant factors. Plants have evolved a complex metabolism that is highly responsive to changes in the environmental conditions and critical for their survival in different habitats. Specialised pathways produce “secondary” metabolites from the primary metabolism that allow plants to tolerate adverse abiotic conditions, defend themselves, and communicate with their surroundings. It is well-known that in plants environmental inputs induce epigenetic changes, including chromatin modifications, that affect differentiation and reproduction, or that are associated with plant acclimation and defense priming. In addition to the CpG methylation found in mammals plants have non-CpG methylation in CHH and CHG contexts. CHH and CHG methylation patterns are generally stable and commonly result in the transgenerational non-mendelian inheritance of silenced “epialleles” (also termed paramutations). This plant-specific non-CG methylation is reversible and highly sensitive to changes in folate-dependent one-carbon metabolism allowing plants to adjust the output of their genomes, and thus their phenotype, to the environmental conditions and pass on this epigenetic information to their offspring. Particularly in plants signaling by reactive oxygen species (ROS) and nitric oxide (NO) is sensitive to environmental conditions, and modulates metabolic pathways and the activities of genes that encode epigenetic enzymes. As ROS and NO are hallmarks of stress responses, they might be important for mediating chromatin dynamics during adaption to environmental stresses, including global warming. Given the existential importance of plants for human civilisation (oxygen production, carbon fixation, food security) this clearly warrants further research. An overview of our current knowledge how metabolism and epigenetic mechanisms are connected in plants is given in the review by Lindermayr and colleages **[18]**.

**7. Metabolic Memory, Epigenetic Inheritance, and Epidemiology**

Finally, it is interesting to know how perturbations in an organism’s environment, such as particular diets that initially have rather short-term effects on metabolism can lead to long-term changes and potentially a memory of the stimulus that might even be transmitted to subsequent generations, considering that the genetic information in the genome is fixed and cannot be changed. This is closely related to the questions of how these processes are linked to human health and whether they could be utilised to treat diseases through manipulating the metabolism.

The review by Bheda explores this question using transcriptional metabolic memory in single celled model organisms as example **[19]**. In these organisms, that need to mainly respond to the availability of different carbon sources, transcriptional metabolic memory that affects later gene expression responses to subsequent exposures to the same stimulus can be stored via changes in chromatin modifications or chromatin architecture, RNAs, and proteins that persist after a transient exposure to a stimulus. Despite being more complex there are examples where such “metabolic memory” is conserved in multicellular organisms. A medically highly relevant example in humans is the metabolic memory of hyperglycemia (exposure to high glucose levels in the blood) that can lead to the development of diabetes long after the glucose exposure levels are back to normal. The hope is that such “metabolic reprogramming” by a transient or sustained change in the diet can rewire metabolic networks by changing gene expression patterns and the proteome/metabolome (i.e. abundance of metabolic enzymes and metabolites) of cells and tissues, and that such interventions may be a path to treat metabolic diseases including diabetes or obesity, and maybe even chronic inflammatory diseases and certain cancers.

Quantitative genetic studies (GWAS - genome-wide association studies) of complex metabolic diseases such as obesity and diabetes hint to the involvement of certain biological pathways, e.g. the central nervous system. However, the contribution of individual disease-linked genetic variants (SNPs - single nucleotide polymorphisms) to the phenotypic traits is typically small, indicating a significant contribution by environmental factors that interact with the genes of an individual through epigenetic mechanisms. As most of the identified SNPs are non-coding the locus-specific mapping of epigenetic traits, such as DNA methylation, chromatin accessibility, and histone modifications (EWAS – epigenome-wide association studies), and gene expression profiles (eQTLs – expressed quantitative trait loci) in tissues and cells linked to diseases is important to identify changes in specific chromatin regions brought about by genetic and environmental factors to understand the etiology of these diseases. An update on high-throughput sequencing techniques and findings that connect metabolic diseases with epigenetic markers is provided by Grundberg and colleagues **[14]**.

From a standpoint focused on human health it is important to ask whether and how information about the prevailing environmental conditions, such as nutrition and diet, can be passed on to the offspring. In addition to genetic information also “epigenetic” information can be passed on to subsequent generations. Well studied examples are the generally stable inheritance of DNA methylation observed in plants that leads to heritable gene silencing or “epialleles” (see above), and the parent-specific epigenetic imprinting of genes found in mammals, although this is erased in each generation. It has become apparent that parental exposure to nutritional challenges and other stressors, such as social stress or toxin exposure, can induce alterations in the germ cells that affect metabolic phenotypes and a number of other traits in the following generation(s) – this includes glucose tolerance, cholesterol and lipid metabolism, body weight, fat distribution, anxiety-related behaviour, and reproductive health. Thereby, information about the environment can be passed on to the offspring, however in most cases only over a limited number of generations. The mechanisms how this epigenetic information is transmitted through the germline (DNA methylation, modifications of histones or protamines, non-coding RNAs, or even the composition of the paternal seminal fluid or conditions in the maternal reproductive tract are in discussion) and how this results in an altered metabolism in the offspring are so far not well understood. The question of what, how, and how much information is transmitted to subsequent generations epigenetically and how it manifests itself is highly relevant from a population genetics and epidemiological perspective, since the commonly transmitted traits seem to be metabolic phenotypes. These topics are discussed in the review by Rando and colleagues **[13]**.

**8. Conclusions**

Overall the emerging links between epigenetics and cellular metabolism are a fascinating and timely research topic with major implications for basic research in various model organisms, but also for the etiology of human diseases - in particular cancer and metabolic diseases. Our aim was to highlight some crucial concepts of how chromatin and metabolism are connected and the implications if this crosstalk goes wrong. We also wanted to raise awareness to some of the major open questions and stimulate discussions.

**Conflict of Interest**

None

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**Figure Legends**

**Figure 1:** Crosstalk between metabolism and the epigenetic machinery. Energy (carbon) sources taken up by cells are converted into ATP and different metabolic intermediates by metabolic enzymes (MEs) and define the metabolic state of a cell. Metabolites such as vitamins, short chain fatty acids (SCFAs) or essential amino acids that feed into the metabolism can also be taken up directly from the environment. ATP is used by chromatin remodelers and many metabolites serve as co-factors or inhibitors of chromatin modifying enzymes. The metabolism and chromatin regulators also serve as “hubs” that funnel extra- and intracellular signals to chromatin in order to generate distinct transcriptional responses. -KG – alpha-ketoglutarate, ATP – adenosine triphosphate, -ox – beta-oxidation, FAD - flavin adenine dinucleotide, NAD+ - nicotinamide adenine dinucleotide, OXPHOS – oxidative phosphorylation, SAM - S-adenosyl-L-methionine, SAH - S-adenosyl-L-homocysteine, TCA – tricarboxylic acid cycle.