Epigenetics: An Intermediary of Environmental Regulation of Metabolism

Andrzej Z. Pietrzykowski1,2*
1Department of Animal Sciences, Rutgers University, USA
2Department of Genetics, Rutgers University, USA

Abstract

Epigenetics fills a gap in our understanding of the interplay between genes and the environment. Recently, major progress has been made establishing that environmental nutritional signals affect an organismal metabolic homeostasis via epigenetic mechanisms. For example, characterization of specific micro RNAs associated with fat and brain tissue along with the determination that fat mass and obesity-associated protein (FTO) functions as a RNA demethylase, change dramatically our understanding of metabolic processes.

Here, we provide a comprehensive review of four major epigenetic mechanisms: chromatin remodeling, histone modifications, DNA methylation and RNA processing, and their regulation by nutrients. A deeper understanding of a complex cellular reaction to nutritional environment seems to be a paramount condition to invent novel, efficient treatment options for the metabolic diseases and could help to curb the epidemic of obesity.

ABBREVIATIONS

FTO, INO80, ISWI, NuRD/Mi-2/CHD, SWI/SNF, SWR1, HAT, HDAC, McCP2, MBD1, MBD2, NAD+, NAMPT, DNMT, SAM, TET, POMC, NPY, AgRP, PPARY, PPARα, PDX-1, PDK1, CPT1, CROT, HADHB, GWAS, RRACH.

INTRODUCTION

It is becoming increasingly recognized that reduction of complex individual differences to the effects of either nature (genes) or nurture (environment) is obsolete. Epigenetics has recently rewritten this binary view and helped us to better understand how intertwined are interactions between genes and environment. In this review we will describe some epigenetic mechanisms, which have been recently indicated as particularly important in regulation of metabolism and a metabolic syndrome, a collection of nutrition-dependent disorders including obesity, hyperglycemia, hyper lipidemia, hyper insulinemia, hypertension and insulin resistance [1].

The term epigenetics was coined as a portmanteau of epigenesis and genetics by Conrad Waddington in 1942, to describe a model of how genes can interact with their environment to produce a phenotype. Initially, it was more of a philosophical concept, however the recent discoveries unraveled several molecular mechanisms underlying epigenetics. In its early stage epigenetics was focused on (meiotical or mitotical) heritability of changes in gene expression without changes in the DNA sequence. Importantly, with the progress in discovering epigenetic mechanisms it became evident that these mechanisms are not limited to the reproductive tissues involved in trans generational heritability, but are also taking place in other somatic organs of a body or in un dividing cells. In either case, it is particularly important to understand that epigenetic mechanisms can provide a bridge between environmental and nutritional signals, and an organismal metabolic homeostasis, allowing the living organisms to continuously adapt to fluctuations in the availability of nutrients and energy resources in their environment.

There are several epigenetic mechanisms discovered thus far, which fall into four categories of post-translational modifications of either DNA, protein or RNA. These include: 1/ chromatin remodeling, 2/ histone modifications, 3/ DNA methylation and 4/ RNA processing. Although these mechanisms initially were studied independently, a growing body of evidence indicates that they may be interconnected. In this review, a short description of each category will precede a more-detailed section focused on recent studies connecting a particular epigenetic mechanism to metabolism and nutrition.

Chromatin remodeling refers to changes in chromatin architecture associated with changes in DNA transcription.
Chromatin is a complex of DNA and associated proteins bundled together into repeating units of nucleosomes. Each nucleosome consists of 147 nucleotides of DNA wrapped around a protein core built of an octamer of protein histones (a pair of each four histones: H2A, H2B, H3 and H4). Chromatin density, which is a function of binding between histone complexes and the DNA, plays a role in regulation of gene expression. For example, in high chromatin density, DNA is tightly wrapped around nucleosomes and thought to be transcriptionally inactive, while in low chromatin density DNA is loosely wrapped around nucleosomes and transcriptionally active. Several specific chromatin remodeling complexes have been found so far: INO80 [2][3], ISWI [4], NuRD/Mi-2/CHD [5], SWI/SNF [6] and SWR1 [3]. Their main role is to orchestrate chromatin remodeling by dynamically regulating three-dimensional arrangement of nucleosomes. During chromatin remodeling the structure, composition or positioning of nucleosomes is changed in the ATP-dependent manner, which reversibly enables (or inhibits) access of the transcription machinery to the core promoter regions of genes: relaxation of chromatin allows for access of transcription factors and RNA polymerase to promote transcriptional activity of DNA, while condensation of chromatin decreases transcription.

Chromatin remodeling is also linked to histone modifications [7]. Covalent modifications of histones forming a core of the nucleosome complex can change chromatin architecture and density.

Histone modifications are governed by special protein complexes, which contain various enzymes modifying post-translationally specific amino-acid side chains within the histones. There are multiple types of histone modifications e.g.: acetylation or methylation. These modifications alter the binding affinity between DNA and histones leading to a change in DNA wrapping around nucleosomes and its accessibility to the transcriptional machinery. For example, histone acetylation appears to decrease nucleosome density, promote chromatin open state and activation of transcription. Histone acetylation is governed by histone acetylases (HAT), while deacetylation appears to decrease nucleosome density, promote chromatin density DNA is loosely wrapped around nucleosomes and thought to be transcriptionally active.

Another process, which influences chromatin structure and gene expression without changes of the DNA sequence is DNA methylation. During DNA methylation methyl groups are added enzymatically to cytosines of the DNA at carbon-5 (C-5) position creating 5-methylcytosines. In somatic cells, cytosine methylation is primarily at CpG dinucleotide context (cytosine precedes guanine at the same DNA strand and they are link by a single phosphate /p/ group). Often, several CpG dinucleotides are clustered forming CpG islands [9]. Cytosine methylation occurring at the CpG islands within promoters of genes can affect expression of these genes. For example, methylated cytosines can be recognized by specialized nuclear proteins called methyl CpG binding domain proteins (MeCP2, MBD1, MBD2 and others).

These proteins can bind to the methylated cytosines, further recruiting the histone deacetylases, which by removing asyl groups from histones as described above can condense and inactivate chromatin. DNA methylation can also affect gene transcription by changing binding of transcription factors [10].

The abovementioned epigenetic mechanisms are taking place in the nucleus of a cell, however other types of epigenetic regulation of gene expression occur in the cellular cytoplasmic compartment. Cytoplasmic epigenetic mechanisms will target protein-coding transcripts (mRNA) modulating their half-lives or efficiency of protein synthesis. One RNA-dependent epigenetic mechanism working this way involves micro RNAs, while another mRNA methylation.

First micro RNA was discovered in mid-1990 [11], but research on micro RNA gain more thrust almost a decade later, accelerating exponentially during the last ten years. Micro RNAs belong to a class of short (17-25 nt long) RNA species, which don't encode proteins but work as mRNA regulators. mi RNAs can regulate mRNA decay and protein translation by binding to the 3'UTR regions of mRNA transcripts based on RNA:RNA complementarity [12]. Typically, base-pairing between micro RNA and its target results in impairment of protein synthesis from this transcript or degradation of the transcript causing in either case decreased production of a specific protein. Interactions between a micro RNA and its target are dynamic, and have been divided into nine, linked mechanisms each with a different kinetic signature [13]. Micro RNAs and micro RNA-related mechanisms are ubiquitous and can be found in viruses, plants and eukaryotes. Many micro RNA species are well-conserved but also each species can have its unique set of micro RNAs. Moreover, micro RNA expression can be tissue- and cell type-specific [14]. Importantly, micro RNA can have a large impact on an overall gene expression due to their ability to target simultaneously several mRNA transcripts. On average, a single vertebrate micro RNA is thought to regulate around 200 transcripts [15].

Aberrant (either higher or lower) expression levels of micro RNAs have been showed to be associated with some diseases, and in some cases a causal link has been proposed [16].

mRNA methylation is another cytoplasmic epigenetic mechanism involving ribonucleic acid. Similarly to micro RNA, the initial discovery of mRNA methylation took place a while ago (in the seventies) and research on mRNA methylation just recently started to gain momentum. It appears that mRNA methylation is a common cellular process involving addition of a methyl group to adenosines of various forms of RNA (both protein coding and non-coding): mRNA, micro RNA, long non-coding RNA and others [17]. The most abundant mRNA modification in eukaryotic cells is the methylation of the nitrogen at position 6 of adenosine bases within mRNA (m'A), however other forms of this modification are also known [17]. m'A methylation can regulate nuclear export of mRNA transcripts and their stability [17]. Since methylation of adenosines has an impact on RNA function but it does not change the RNA nucleotide sequence per se, these modifications occurring on various forms of transcribed RNA species are called collectively epitranscriptomics.

Many of these epigenetic processes have been described
Chromatin remodeling and metabolism

Chromatin remodeling is an epigenetic mechanism involving a dynamic regulation of chromatin architecture, which subsequently will lead to the changes in gene expression. There is very little research on this high level regulation of gene expression by nutrition. This is quite a surprise considering that the information about nutritional environment or energy metabolism can be conveyed into next generations, and that this process requires cell divisions (meiotical and/or mitotical). Interestingly, all five main families of chromatin remodelers distinguished so far: INO80, ISWI, NuRD/Mi-2/CHD, SWI/SNF and SWR1, share a common ATPase domain. This domain allows them to produce energy to reposition nucleosomes along DNA [18] - a mechanism important for several aspects of cell division (chromosome assembly and segregation, DNA repair and replication, cell cycle progression). Importantly, uncontrolled cell divisions are thought to be a crucial mechanism of the development and progression of several cancers, thus chromatin remodelers are intensively studied in the cancer field, including development of new therapeutic strategies [18]. Establishment of a mechanistic link between nutrition and chromatin remodelers may allow to consider the use of specific nutrients and diet in cancer prevention and treatment.

Histone modification and metabolism

In contrast to chromatin remodeling, research focused on the role of post-translational modifications of histones as an epigenetic response to the environment and its nutritional composition is very extensive. Post-translational modifications of histone proteins include glycosylation, methylation, acetylation and others [19]. These modifications are thought to be reversible [20] and conducted by histone-modifying enzymes, which can either add or remove a specific modifying group, (e.g. an acetyl group is added by acetylases and removed by deacetylases). Interestingly, almost all histone-modifying enzymes use crucial metabolites of core metabolic pathways as substrates [20]. Moreover, it seems that activity of histone-modifying enzymes depends on the relative abundance of metabolites, which suggests that these enzymes can serve as sensors of metabolism, and provide a direct link between a metabolic state and an epigenetic mechanism of gene expression regulation [20]. Amount of uridine diphosphate (UDP)-glucose reflects the blood glucose levels and is a product of an alternative glucose metabolism (the hexosamine pathway). UDP-glucose serves as a substrate for O-GlCNacylation of histones (attachment of a glucose group through O-linked N-acetylglucosamine to serine or threonine residues). This process is controlled by enzymes called O-GlcNAc transferase (OGT, UDP-glucose addition) and O-GlcNAcase (OGA, UDP-glucose removal) [21].

For histone methylation a methyl group from the S-adenosylmethionine (SAM) is used by histone methyltransferases (HMTs) to methylate histone H3 [22]. Although histone methylation is thought to be pretty stable, demethylation of histones can also occur and is conducted by a separate group of enzymes called demethylases [23][22]. Interestingly, a single methylation of histone H3 on lysine 27 (H3K27) or dimethylation of this histone at lysine 9 (H3K9me2) is associated with gene repression, while a triple methylation of the same histone on lysine 4 (H3K4me3) is associated with gene activation [24]. However, that is not all. Methylation can also happen at additional places on histone H3 or other histones making this epigenetic mechanism truly complex [24, 25].

Histone acetylation is strongly correlated to cell metabolic state. Acetyl-CoA is generated from ingested nutrients through anabolic mechanisms and serves as a universal donor for acetyl groups. In both yeast [26, 27] and mammalian cell culture [28] histone acetylation primarily depends on glucose-derived pools of acetyl-CoA. During high glucose states this histone modification can increase expression of genes regulating cellular proliferation, lipogenesis and adipose differentiation [29]. Interestingly, fasting also leads to changes in free acetyl-CoA levels and marked increase in lysine acetylation of many mitochondrial proteins [30]. This acetylation could also potentially affect nuclear histones.

The opposite reaction, histone de-acetylation, is also under an enzymatic control and is linked to metabolism. The removal of acetyl groups from histones is governed by histone deacetylases (HDACs). One of the most known HDACs are sirtuins [31]. Sirtuins use as a co-factor NAD⁺, which is a known energy carrier [32]. Sirtuins protein levels are relatively stable, however the enzymatic activity of sirtuins is affected by levels of NAD⁺, which in turn depends on the levels of nicotinamide phosphoribosyl transferase (NAMPT). The activity of this enzyme is under the tight control of the circadian rhythm [32, 33]. However its regulation (or regulation of NAD⁺) by metabolic conditions still needs solid evidence. Nevertheless, it has been shown that glucose starvation leads to increase in the amount of NAD⁺, sirtuin activation, deacetylation of histone H3K9 at the loci of ribosomal genes, which results in decreased production of ribosomes, a hallmark of energy conservation.

DNA methylation and metabolism

DNA methylation is an epigenetic mechanism studied extensively in developmentally-relevant meiotic and mitotic processes like genetic imprinting and cell differentiation [34], however it can also occur post-mitotically [35]. DNA methylation is carried out by specific enzymes, called methyltransferases (DNMTs), which transfer a methyl group from a methyl group donor to cytosine at CpG dinucleotide in a DNA strand. The main methyl group donor is S-adenosylmethionine (SAM), a product of one-carbon metabolism of ATP and an aminoacid methionine [36]. Methylone is in turn a methylation product of aminoacid glycine and tetra hydrofolate, a derivative of folate (vitamin B6), which serves as the ultimate source of a methyl group [37]. This chain of methyllations links nutrition and metabolism to DNA methylation [37, 38]. It is worth mentioning that even though DNA methylation is thought to be a stable epigenetic modification, it has been shown recently that methyl groups can be removed from during physiological conditions like development or have been linked to pathology - e.g. cancer. Are these processes important for environmental regulation of gene expression, particularly genes involved in metabolism? I will provide overview of the most recent literature indicating that each of these epigenetic mechanisms is involved in metabolism and possibly in pathogenesis of some metabolic diseases.
DNA cytosines [39]. This active process is governed by ten-eleven transformation (TET) enzymes, which oxidize 5-methylcytosines allowing for their subsequent base excision repair [40]. Notably, some metabolites of the Krebs cycle, which produces energy from nutrients, can regulate TET enzymatic activity [41].

Weight gain and obesity is the outcome of an energy imbalance, namely an increased food intake and/or decreased energy expenditure [42]. A fundamental role of this process is played by the adipose tissue-brain axis [43]. Both tissues are connected by feedback loop mechanisms.

Adipocytes, serve as a main fat reservoir, and release a hormone called leptin proportionally to the amount of accumulated fat [44]. Leptin acts on two types of neurons located in the hypothalamic arcuate nucleus: it stimulates anorexigenic neurons to transcribe pro-opiomelanocortin (POMC) gene, and it inhibits orexigenic neurons decreasing transcription of neuropeptide Y (NPY) and Agouti-related peptide (AgRP) [45]. Balance between activities of these neurons is one of the main contributors of appetite, food consumption and energy homeostasis [45, 46]. DNA methylation regulates expression of POMC gene. In humans in tissues non-expressing POMC the gene promoter is methylated, while POMC promoter hypomethylation is observed in tissues expressing POMC, like the hypothalamus [47]. Impaired expression of POMC gene in this brain structure is associated with obesity [48], and aberrant methylation of the POMC promoter seems to play a role in it. Increased methylation leads to obesity in mice [49]. Interestingly, as shown in rats, early postnatal overfeeding leads to hypermethylation of hypothalamic POMC promoter and predisposition to obesity [50]. Surprisingly, maternal peri-conceptual under nutrition hypomethylates the hypothalamic POMC promoter in the offspring which is also associated with obesity [51].

The reward pathway of the central nervous system is important in regulation of food intake and its malfunction contributes to the development of obesity. The major neurotransmitter of the reward pathway is dopamine, which is released upon feeding to induce a hedonic feeling of pleasure or satiety [52]. The reward system is often disturbed in addiction to either alcohol [53] or drugs of addiction [54]. This prompted to draw parallels between mechanisms of addiction and mechanisms of obesity [55], including epigenetic factors. Kenny and colleagues showed that in rats, obeseogenic, high-fat diet causes hypermethylation of the promoters of the dopamine transporter and tyrosine hydroxylase, a key, rate-limiting enzyme of the dopamine synthesis. These epigenetic marks were associated with decreased expression of these genes and overall decrease in the potency of the dopaminergic pathway, suggesting that more stimulation of this pathway (by hyperphagia) may be necessary to evoke a sufficient feeling of reward. Hyperphagia often leads to weight gain and obesity.

DNA methylation is also an important regulator of adipocyte tissue. The adipose tissue harvested from the obese mice was, in general, less methylated than the adipose tissue of control, normal-weight mice [56]. Recent study by Drong and colleagues [57] showed presence of hundreds of methylation quantitative trait loci present in the adipose tissue. Increased mass of the adipose tissue, a hallmark of obesity, is the result of adipocyte hypertrophy and/or hyperplasia [58]. As mentioned above, adipocytes release leptin proportionally to their amount and size, thus providing a gauge of the amount of fat in the organism. Importantly, expression of leptin in adipocytes is regulated by DNA methylation of leptin’s promoter [59]. Can diet change methylation status of the leptin promoter? This fundamental question was recently answered by Milagro et al. [60]. Retropertitoneal adipocytes isolated from rats, which gained weight by consuming high-fat cafeteria diet for 11 weeks, showed a significant methylation of a specific site in the leptin’s promoter. These animals had also lower levels of circulating leptin. The important question still remains whether this mechanism is applicable to humans. It would be of interest to determine the evolutionary conservation of this site, its presence in humans, and the effect of Western diet on the methylation status of this site in human populations and the associated risk for metabolic syndrome and associated disorders.

Adipocyte differentiation and function is under control of peroxisome proliferator-activated receptor γ (PPARγ), which expression depends on a methylation status of its promoter [61]. Importantly, in the mouse model of diabetes the visceral adipose tissue of the diabetic animals shows increased PPARγ promoter methylation leading to the lower expression of PPARγ mRNA [56].

PPARγ or leptin are not the only genes, which methylation is regulated in adipocytes. As mentioned there are hundreds of methylation sites present in the adipose tissue [57]. Interestingly, global methylation of adipocyte DNA can be influenced by exercise resulting in changed expression of several genes involved in adipocyte metabolism [62, 63]. Notably, these genes do not include PPARγ or leptin. Thus, methylation of other genes may be a key in the accumulation of fat by adipocytes and in development of obesity.

**miRNA and metabolism**

Proper gene expression in response to nutrition and various metabolic stimuli is critical for maintaining homeostasis. A major post-transcriptional regulation of gene expression is governed by micro RNAs, short, single-stranded RNA products of non-coding DNA [64], micro RNAs have been shown to regulate several key cellular processes across the evolutionary landscape from simple to complex organisms [65], and their dysregulation has been linked to many diseases [66]. There is a rapidly growing body of evidence that micro RNAs can also play a fundamental role in regulation of metabolic processes.

Several micro RNAs regulate insulin synthesis and release from pancreatic β cells [67] as well as survival of these cells [68]. Other micro RNAs, distinct for each tissue, are involved in glucose and lipid homeostasis in hepatocytes and adipocytes [69]. They also regulate differentiation of adipocytes [70]. The list of metabolism-relevant micro RNAs expressed in specific tissues is growing every day, however certain micro RNAs are particularly worth mentioning. miR-375 is probably the best established micro RNA involved in glucose homeostasis. This micro RNA is expressed in pancreas, particularly high in the islet of Langerhans [71]. Glucose affects levels of miR-375, which controls expression of PDX-1, a major transcriptional
factor regulating β cells proliferation. miR-375 additionally targets PDK1, a key regulator of insulin gene expression as well as myotropin, a modulator of insulin release [72]. This specific multi-targeting is a characteristic feature of micro RNA function and places miR-375 in a centre of glucose responsiveness of β cells. Therefore, it is not surprising that miR-375 deletion leads to glucose intolerance, hyperglycemia, diminished number of β cells and a severe diabetic state [73]. miR-375 holds a great promise for future therapeutic development focused on diabetes mellitus. Another micro RNAs, miR-103 and miR-107 are expressed in many tissues and are involved in insulin sensitivity [74]. Importantly, a global silencing of these micro RNAs resulted in improved insulin sensitivity and glucose homeostasis [75], making them an attractive potential therapeutic.

Metabolism of lipids, including cholesterol, is dynamically regulated by nutrients and dysregulation of lipid homeostasis is associated with severe diseases including obesity, diabetes mellitus, atherosclerosis and others. There are several micro RNAs involved in lipid metabolism. miR-122 is a prominent one: it is expressed abundantly in the liver and targets a number of key genes involved in cholesterol [76] and fatty acids biosynthesis [77]. Importantly, knockdown of miR-122 in the liver improved liver steatos is in diet-induced obesity [77] and increases expression of genes involved in lipid biogenesis without liver toxicity [78]. miR-33 is another attractive micro RNA with therapeutic potential involved in lipid homeostasis. miR-33 targets some of the enzymes (Carnitine palmitoyltransferase 1 /CPT1a/, carnitine O-octanoyltransferase /CROT/ and acetyl-CoA acyltransferase /HADHB/) belonging to the β-oxidation pathway of fatty acids [79]. Although hepatocyte-specific miR-33 knock-down data are not available, over expression of miR-33 in hepatocytes reduced expression of miR-33 target genes leading to decreased β-oxidation of fatty acids [80]. It will be of great interest to determine whether there is a connection between nutrition and transcriptional regulation of these micro RNAs, namely whether specific nutrients can modulate expression of miR-122 and miR-33 in hepatocytes. This area of research could provide an attractive venue for “nutri-therapeutics”.

miR-122 and miR-33 are not the only ones involved in metabolic processes. Comparative micro RNA profiling of micro RNAs expressed in human adipocytes showed that miR-519d is not only over expressed in these cells in obese adults but also it targets peroxisome proliferator-activated receptor α (PPARα), a transcription factor of fundamental role in fatty acid homostasis in adipocytes [81]. It is worth to mention that, a thorough micro RNA profiling showed at least over twenty different micro RNAs involved in regulating adipogenesis [82]. Moreover, comparison of different types of adipose tissues in swine showed that there are significant differences in micro RNA expression between visceral and subcutaneous adipose tissues [83]. Similarly, micro RNA expression differed between abdominal subcutaneous and intra-abdominal adipose tissue in obese humans [84].

RNA methylation and metabolism

Very recent and probably the most fascinating breakthrough in epigenetics was a discovery of the role of the fat mass and obesity-associated protein (FTO) in metabolism and obesity. In 2007 and following years a series of papers reported, based on genome-wide association studies (GWAS), an association of SNPs located in the FTO gene with body mass index [85, 86], and the risk of child and adult obesity [85, 87-89]. At that time the role of the FTO gene product was unknown. It was just recently established that the FTO protein functions as a demethylase of internally methylated RNA adenines (m6A = internal N6-methyladenine) of RNA [90].

Modification of RNA by various types of methylation has been known for a while [91], however role of these modifications was unclear [91, 92]. m6A methylation is the most abundant internal modification of eukaryotic mRNA with estimated 0.3% of the total adenosine residues having this modification [93]. m6A profiling combined with next generation sequencing revealed that at least 7,000 mRNA transcripts and 300 non-coding transcripts have this modification [94]. On average, there are three to five m6A per RNA transcript in a mammalian cell [93], which likely is an underestimate. m6A methylation is happening preferentially within the m6A methylation consensus sequence (RRACH: R – a purine base /adenine or guanine/, A – m6A Adenine, C – Cytosine, H – a non-guanine base), which is located primarily within stop codons, long exons and 3’UTRs of RNA transcripts [95]. Presence of m6A on 3’UTRs is particularly intriguing due to 3’UTRs serving as primary targets of micro RNAs. Interestingly, although m6A’s are associated with micro RNA binding sites they are not present within the sites but at nearby locations, rising a possibility of recruitment of specific binding proteins modulating interaction of micro RNAs with 3’UTRs [96].

m6A methylation is governed by an enzyme called N6-adenosine methyltransferase (RNA m6A writer) and it is happening co-transcriptionally during pre-mRNA processing in the nuclear speckles [97].This epigenetic stamp is carried with a mature mRNA exported to the cellular cytoplasm. Importantly, this modification is reversible and dynamically regulated. FTO is an enzyme, which can remove m6A stamps from RNA transcripts (RNA m6A eraser) [96]. This process is most likely taking place during early stage of transcript processing as indicated by FTO presence within the nuclear speckles [90].

What are possible effects of methylation or de-methylation of RNA transcripts? One possibility is that these modifications could modulate affinity of certain RNA-binding proteins to the transcripts and thus regulate transcript processing, half-life or amount. This regulation could lead to downstream effects, e.g. in case of protein-coding transcripts, it can change amount of protein produced from the transcript. Another intriguing possibility is that methylation close to the micro RNA binding sites could affect micro RNA binding to the transcripts with the similar ramifications. Testing these possibilities will be an exciting area of research, particularly regarding nutrient-dependent regulation of RNA transcripts. Indeed, some data started to emerge. FTO is most highly expressed in the brain, particularly in a brain region called arcuate nucleus [98], a cluster of neurons located in the mediobasal hypothalamus, containing neuroendocrine cells controlling endocrine functions of anterior pituitary, as well as centrally projecting neurons, which as parts of the oxytocic and anoxicogenic pathways, are involved in regulation of appetite and food intake [99, 100]. Nutritional status affects expression levels of the FTO gene in arcuate neurons: fasting decreases, while
consumption of high-fat diet increases amount of FTO transcripts [98]. Intriguingly, FTO expression is regulated by glucose and essential amino-acids but not by non-essential amino-acids or other nutrients [101]. Importantly, Hess and colleagues [102], established a connection between FTO, nutrient sensing and the brain reward system. Using FTO KO mice, global m’A mRNA modifications and next-generation sequencing they showed that in regions involved in the reward system, e.g. striatum, FTO controls m’A methylation of several key transcripts important in dopamine signal transmission, neuronal activity and behavioral response to cocaine.

Thus, rather unexpectedly, an epigenetic factor became one of the most important nutrient sensors and a molecular bridge between food and reward.

CONCLUDING REMARKS, FUTURE CHALLENGES

An increase in the body weight due to excess of adipose tissue raises a big concern because of its association with several serious diseases, called sometimes collectively the metabolic syndrome [103]. Moreover, this phenomenon is currently of epidemic proportions and on the rise in many Western [104] and other countries [105-107]. Fortunately, due to a fast progress of basic, translational and clinical research we can now accept with confidence that molecular features of the metabolic syndrome include complex changes in the epigenetic state of promoters of genes encoding elements of the metabolism-controlling systems. Thus, metabolic syndrome is, at least partially, an epigenetic disease. Notably, not one but several distinct epigenetic mechanisms taking place in both, nuclear and cytoplasmic compartment of a cell, and intertwined into a complex network seem to play a key role in the development of the metabolic syndrome and associated diseases.

It is important to realize that although the metabolic syndrome is most commonly associated with increased mass of the adipose tissue as a result of adipocyte hypertrophy and hyperplasia [108, 109], epigenetic mechanisms are simultaneously taking place in many other tissues and organs (e.g. liver, pancreas, brain), and are either directly or indirectly involved in the development of the metabolic syndrome associated diseases.

Deep understanding of complexity of epigenetics in the metabolic syndrome is not only crucial for comprehension of the pathogenesis of these disorders but also fundamental in designing effective long-term therapeutic strategies. Currently, re-gain of lost weight after diet- [110] or surgery-dependent [111] interventions are still way too high, reaching around 80%. Let’s hope that focus on epigenetics could bring these numbers substantially down, in part due to another advantage of epigenetics – a personalized approach, allowing to fit therapeutic options into the epigenetic mold of an individual.

ACKNOWLEDGEMENTS

This work was partially funded by a NIH/NIAAA Award (R01-AA017920), a NIH/NIAAA Career Development Award (AA01748) and a Pilot Project from the NIH/NIAAA INIA-West Consortium (AA020895) to AZP.

Support

NIH 5R01AA017920, K08AA01748, INIA-West Pilot Project and Rutgers University start-up funding to AZP

REFERENCES

8. Wozniak GG, Strahl BD. Hitting the ‘mark’: Interpreting lysine methylation in the context of active transcription. Biochim Biophys Acta 2014;.
21. Hart GW, Hausley MP, Slawson C. Cycling of O-linked beta-N-


73. Närä AM. MiRs with a sweet tooth. Cell Metab. 2011; 14: 149-150.


