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REVIEW ARTICLE

Environmental toxicants, incidence of degenerative diseases, and therapies from the epigenetic point of view

Mahshid Hodjat[1,4] · Soheila Rahmani[1] · Fazlullah Khan[1,2,3] · Kamal Niaz[1,2,3] · Mona Navaei–Nigjeh[1,5] · Solmaz Mohammadi Nejad[1] · Mohammad Abdollahi[1,3]

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Abstract Epigenotoxicology is an emerging field of study that investigates the non-genotoxic epigenetic effects of environmental toxicants resulting in alteration of normal gene expression and disruption of cell function. Recent findings on the role of toxicant-induced epigenetic modifications in the development of degenerative diseases have opened up a promising research direction to explore epigenetic therapy approaches and related prognostic biomarkers. In this review, we presented comprehensive data on epigenetic alterations identified in various diseases, including cancer, autoimmune disorders, pulmonary conditions as well as cardiovascular, gastrointestinal and bone disease. Although data on abnormalities of DNA methylation and their role in the development of diseases are abundant, less is known about the impact of histone modifications and microRNA expressions. Further, we discussed the effects of selected common environmental toxicants on epigenetic modifications and their association with particular abnormalities. A number of different environmental toxicants have been identified for their role in aberrant DNA methylation, histone modifications, and microRNA expression. Such epigenetic effects were shown to be tissue-type specific and highly associated with the level and duration of exposure. Finally, we described present and future therapeutic strategies, including medicines and dietary compounds for combating the toxicant-induced epigenetic alterations. There are currently seven histone deacetylase inhibitors and two DNA methyltransferase inhibitors approved for clinical use and many other promising candidates are in preclinical and clinical testing. Dietary compounds are thought to be the effective and safe strategies for treating and prevention of epigenetic pathophysiological conditions. Still more concentrated epigenetic researches are required for evaluation of chemical toxicity and identifying the causal association between key epigenetic alteration and disease.

Keywords Epigentic changes · Environmental exposures · Epigenetic machinery · Histone modification · Therapy · Nutrition

✉ Mohammad Abdollahi
mohammad@tums.ac.ir

1 Toxicology and Diseases Group, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran

2 International Campus, Tehran University of Medical Sciences (IC-TUMS), Tehran, Iran

3 Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

4 Dental Research Center, Tehran University of Medical Sciences, Tehran, Iran

5 Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Evaluating and monitoring the potentially hazardous effects of environmental toxicants on human health are important issues of the present industrial era. Ubiquitous exposure to the vast number of known and unknown synthetic toxicants has become an inevitable part of the modern life that could be responsible for the imbalance of normal physiological status and the cause of serious diseases and abnormalities in individuals (Hodjat et al. 2016; Khan et al. 2016; Koopaei and Abdollahi 2017; Niaz et al. 2017). Therapeutic approaches to intervene the toxicant-induced

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disorders basically rely on understanding the mechanism of toxic action at molecular and cellular level. It is known that environmental toxicants could exert their disrupting effects through genotoxic and non-genotoxic mechanisms. Epigenetic modifications as the non-genotoxic mechanism of toxicant-induced health effects have recently opened a new window of research in toxicological studies.

In general, epigenetic is defined as any stable and heritable changes in the chromatin structure that can result in alteration of gene expression and appearance of the abnormal phenotype. Changes in genomic structure are mediated through enzymatic chemical modifications on DNA structural bases and histone proteins that consequently influence the gene accessibility and alter DNA transcription (Loscalzo and Handy 2014). Another mode of epigenetic gene regulating is mediated by non-coding RNA, the functional DNA transcripts that are not translated into protein and have a role in gene suppression or activation at transcriptional and post-translational levels.

Studies have shown that epigenetic changes play a critical causative role in the etiology of many diseases including autoimmune disorders, pulmonary conditions, and cardiovascular diseases as well as different cancer types. So far, many researches have been conducted to reveal the mechanisms of epigenetic changes involved in the malregulation of genome expression and induction of diseases (Jeong et al. 2014). Environmental agents are extrinsic factors that modulate the aberrant changes of epigenetic pathways. Tobacco smoke, metal ions, bisphenol A, benzene, alcohol and many other toxicants along with their genotoxic potential are shown to be the inducer of epigenetic alterations.

Although our knowledge on the functional mechanisms of environmental epigenomic modulators is still not adequate, fascinating investigations have emerged to find the factors that could reverse the abnormal epigenetic changes; therefore alleviate or remove the abnormal phenotypes. These factors could be grouped into therapeutic and dietary chemopreventive agents. In this review, we presented comprehensive data on human degenerative diseases recognized to have epigenetic links and attempted to collect the mechanistic data on the studied epigenetic events related to such abnormalities. There is a growing list of literature linking the abnormal epigenetic pattern to the exposure to environmental factors. Therefore, we focused on selected environmental toxicants with different epigenetic effects to show the wide range of epigenetic mechanisms that could be affected by toxic substances. We further discussed current therapeutic approaches and drugs available to adverse abnormal epigenetic changes. Also, we reviewed the current information on some dietary chemopreventive agents that able to affect epigenetic mechanisms.

Mechanisms of epigenetics: an overview

Epigenetic regulation of gene expression is a complex process in which different mechanisms interact individually or synergistically to affect gene expression. The epigenetic factors could change chromatin structure in the way that inhibits or induces transcription machinery functions without changing the DNA sequence (Fig. 1).

DNA methylation

Methylation of DNA has been among the frequently studied epigenetic modifications. This reversible chemical process involved the covalent addition of a methyl group to the cytosine C5 carbon side-chain leading to the formation of 5-methylcytosine (5-mC). In somatic cells, the 5-mC are mostly occuring at cytosine nucleotide followed by guanosine, where creating CpG dinucleotides. The applied methyl groups change the structure of DNA major groove

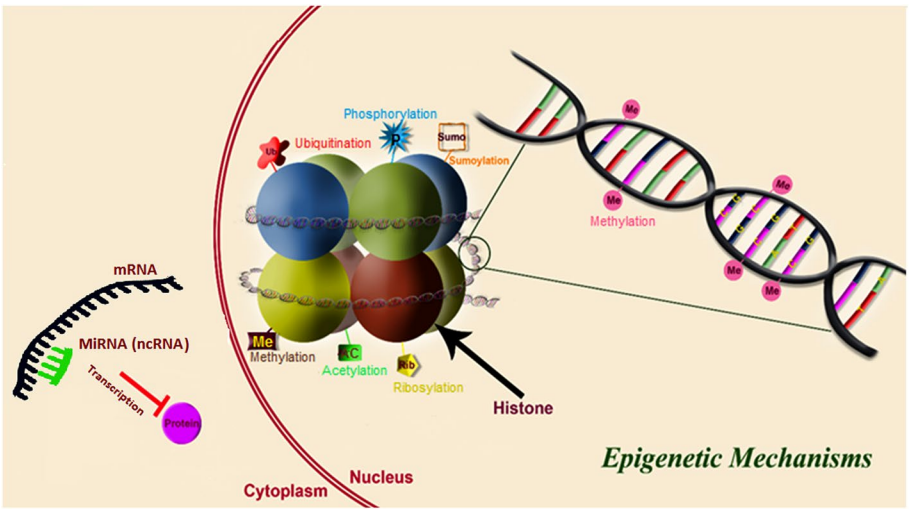

Fig. 1 Epigenetic mechanisms

and inhibit the DNA transcription, and therefore impair gene function (Weinhold 2006).

Family members of DNA methyltransferase (DNMTs) including DNMT1, DNMT2, DNMT3L, DNMT3a and DNMT3b are responsible for the transfer of methyl group to DNA cytosine (Sun et al. 2015). Based on their function, they are categorized into two groups: maintenance and De novo enzymes. De novo DNMTs place the methyl group on unmethylated CpG sites whereas the maintenance DNMTs add methyl group to the hemimethylated CpG (Feng et al. 2010).

Histone modifications

Histone modifications have an important role in chromatin remodeling and gene regulations. Based on the type of modifications, nucleosomal histones are covalently marked by different chemical groups at specific amino acids of their tail region. The most studied histone modifications include methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation (Loscalzo and Handy 2014). In addition to covalent epigenetic modifications, histone clipping are found to be involved in the N-terminal cleavage of histones tail and alteration of gene expression (Santos-Rosa et al. 2009).

Histone methylation

The reaction is mediated by methyltransferase enzyme involved in adding the methyl group to the amino groups of specific lysine and arginine residues (Weinhold 2006). As opposed to the methyltransferase activity, demethylase catalyzes the removal of methyl groups and therefore reverses the epigenetic influence on specific gene expression. The lysine residues are able to be mono-, di-, or tri-methylated. Depending on the type of methylated histone and targeted lysine residue and also the degree of methylation, histone methylation is associated with silencing and activating of gene expression. It was shown that trimethylation of lysine 4 on histone H3 of genome promoter (H3K4me3) is mostly associated with active expression, while trimethylation of the same histone on lysine 9 and 27 (H3K27me3, H3K9me3) is contributed to gene suppression (Chen et al. 2015a).

Histone acetylation

One of the major histone modifications in eukaryotic cells for regulation of gene expression is acetylation that catalyzed by histone acetyltransferases (HATs) such as sirtuin family. While histone acetylation has shown to be associated with active gene expression there are histone deacetylase enzymes (HDACs) that function to remove the acetyl group and therefore involved in gene suppression (Lau et al. 2000; Herberg et al. 2015).

Histone ubiquitination

Histone ubiquitination and its role in cellular function have been the focus of research interest for last decades. Ubiquitin ligases are actively involved in adding ubiquitin units to the NH3+ group of lysine residues; resulted in the formation of mono and polyubiquitinated histones. The role for ubiquitination of specific histone residues and the related pathways are emerging. Accordingly, it was shown that H2B monoubiquitination is an important histone modification implemented in gene transcriptional regulation and remodeling of chromatin organization (Turco et al. 2015).

Histone phosphorylation

Phosphorylation and dephosphorylation of histones are the dynamic modification process mediated by kinases and phosphatases, respectively. Threonines, serines, and tyrosines represent the predominant targets for phosphatases activity (Nowak et al. 2003). Phosphorylation of histones has divergent effect on gene expression and are affected highly by cross-talk with other epigenetic modifications (Rossetto et al. 2012).

Non-coding RNA

Non-coding RNAs (ncRNAs) are the group of functional RNA molecules which are not translated to protein. They are categorized into two subgroups based on their size: the short ncRNAs (<30 nucleotides) and the long ncRNAs (>200 nucleotides). ncRNAs play role in histone modifications, chromatin formation, targeting DNA methylation and gene silencing. Their regulatory role in gene expression is related to both transcriptional and post-transcriptional level. MicroRNAs (miRNAs) exert their effect through binding to the messenger RNAs directly which results in the cleavage, degradation or block translation. Similarly, short interfering RNAs (siRNA) act as a mediator in post-transcriptional gene silencing (PTGS) (Esteller 2011). Studies also demonstrated that siRNAs are the potent inducer of heterochromatin formation. Piwi-interacting RNAs (piRNA) are the largest family of short ncRNAs acting as the suppressor of gene expression and suppress the activity of transposon in cells (Weinberg and Wood 2009). LncRNAs are able to make complex with chromatin-modifying proteins which result in chromatin remodeling (Kung et al. 2013).

Diseases implicated in epigenetics

Disruption in epigenetic regulatory pathways can cause incorrect gene expression leading to the development of epigenetic diseases (Lu et al. 2015). The aberrant DNA

methylation and histone covalent modifications, as well as alteration in the expression of ncRNA, have been well evidenced in a wide range of pathophysiological conditions including autoimmune diseases, cancer, cardiovascular disorders, and many other degenerative abnormalities (Hirst and Marra 2009; Paul and Tollefsbol 2014).

Recent epigenetic findings have extended our understanding of the causal mechanism of autoimmune diseases and provided clues that link environmental factors with the etiology of related disorders. In fact, changes in DNA methylation of particular genes have been frequently reported in systemic lupus erythematous (SLE), rheumatoid arthritis and multiple sclerosis (MS) (Javierre et al. 2008; Koch et al. 2013; Zouali 2014; Zufferey et al. 2014; Long et al. 2016). Balade et al. showed a significant lower DNA deoxymethylcytosine content of CD4+ T cell in SLE patients compared to the control group (Balada et al. 2008). Although their experiments addressed no significant changes in mRNA expression of the DNMTs, some studies showed that DNMT1 expression is down-regulated in peripheral blood mononuclear cell of MS patients as well as lymphocytes of SLE that might be associated with aberrant methylation of their gene promoters (Lei et al. 2009; Calabrese et al. 2014). Therefore, changes in DNA methylation could be attributed to the changes in DNMT expression. Histone modification is another epigenetic regulatory factor that its role has started to become clear in immune disorders. Besides the chemical modifications, the aberrant expression of microRNAs has been implicated in MS and other autoimmune diseases through their modulation of protein expression and function of inflammatory pathways (Table 1) (Stanczyk et al. 2008; Zhou et al. 2008).

Various studies have proved the role of epigenetics in the pathogenesis of chronic obstructive pulmonary disease (COPD), asthma and other pulmonary disorders. COPD is a progressive lung disease that can lead to severe airways obstruction and emphysema. Abnormal DNA methylation and decrease in histone deacetylase activity have been frequently reported in COPD patients and were associated with both severity and maintenance of diseases (Kabesch and Adcock 2012; Zong et al. 2015). While HDACs play a key role in the suppression of inflammatory genes expression, their activity was reduced in alveolar macrophages of COPD patients resulted in the amplification of inflammatory response. Such mechanism has also been reported in severe asthma conditions. Furthermore, it was shown that histone methylation and acetylation of particular genes such as the Notch1 gene promoter of lung CD+4 T cell increased significantly in asthma and COPD cases accounting for the aberrant changes in the expression of histone acetyltransferase P300, PCAF genes and subsequent downstream protein activation including HDACs (Kabesch and Adcock 2012; Cui et al. 2013).

Aberrant epigenetic alteration is an emerging cause of cardiovascular disorders and cardiovascular risk factors such as hypertension. Accordingly, increase in DNA methylation of *ALU* in leucocyte was shown to be associated with the prevalence of different cardiovascular diseases (Kim et al. 2010). Many studies also identified the altered methylation of promoter sites of key pathogenesis-related genes such as Monocarboxylate transporters and Hydroxysteroid 11-Beta Dehydrogenase 2 (Zhu et al. 2005; Friso et al. 2008). However, the detailed underlying epigenetic mechanism that involves in the etiology of the cardiovascular disorder is unknown.

Recently, the crucial role of miRNAs in the biology of cardiogenesis and development of numerous cardiovascular diseases has been demonstrated (Udali et al. 2013). There are also strong evidence that particular microRNAs could apply as biomarkers for diagnosis and prognosis of heart failure and acute myocardial infarction (AMI) (Nishiguchi et al. 2015).

Changes in DNA methylation patterns and histone marks have also been evidenced in many neurological diseases (Table 1). Hypermethylation of glucocorticoid receptor (NR3C1) and brain-derived neurotrophic factor (BDNF) promoters in major depression disorders, voltage-gated potassium channels (KCNQ3) promoter in bipolar and extracellular matrix glycoprotein reelin (RELN) promoter in epilepsy are the examples of detected neurological abnormal DNA marks (Onishchenko et al. 2008; Guidotti and Grayson 2011; D'Addario et al. 2012; Kaminsky 2014). There are also many studies on histone modifications and their influence on the expression of genes involved in the development of neurological disorders (Mastroeni et al. 2015; Ganai et al. 2016).

Epigenetic modifications are likely to be detected in many other disorders related to the gastrointestinal system (Ventham et al. 2013; Kelly and Alenghat 2016), skin (Shi et al. 2013; O'Rielly and Rahman 2015) and bone (Takahashi et al. 2015; Baud'huin et al. 2017).

In addition to all above, the emerging role of epigenetics in cancer initiation and progression has currently become the focus of many research studies. The cancer epigenome is characterized by global changes in DNA methylation and histone modification patterns as well as profound changes in non-coding RNA expression (Sharma et al. 2010). Changes in global DNA methylation and site-specific hypo/hypermethylation of particular genes have been well recognized in different types of cancers (Sharma et al. 2010). Loss of DNA methylation of oncogenes such as MAPSIN, R-Ras, S-100 results in their activation that plays crucial role in the cancer development (Wilson et al. 2007; Sharma et al. 2010). Also, epigenetic studies on different neoplastic disorders have shown

Table 1 A summary of the relevant epigenetic modifications involved in the etiology of a variety of diseases

Disease	Epigenetic dysregulation			References
	DNA methylation	Histone modification	Non-coding RNA	
Autoimmune disorders				
Systemic Lupus Erythematous (SLE)	Global DNA hypomethylation Hypomethylation of IL-6 gene in CD4+ T and B cells ↓ DNMT1 expression in lymphocytes	Global hypoacetylation of H3/4 Hypomethylation of H3K9 in CD4+ T cell ↓ HDAC2, HDAC7, KMT1B, KMT6	↓ miR-21, miR-25, miR-125a, miR-146a, miR-148, miR-186 ↑ miR126, miR21, miR148	Zouali (2014), Miceli-Richard (2015), Balada et al. (2008), Lei et al. (2009)
Rheumatoid arthritis (RA)	Hypermethylation of DR3 in synovial cells ↓ DNMT1 expression in synovial cells Unmethylated CpG islands within IL-6 promoter region Hypermethylationof Foxp3	↓ HDAC activity Phosphorylation of H3	↑ miR-155, miR-146=	Zouali (2014), Zufferey et al. (2014), Stanczyk et al. (2008), Le Dantec et al. (2015)
Multiple sclerosis (MS)	Hypomethylation of Peptidylargininedeiminase PAD2 (leading to citrullinated myelin) ↓ DNMT1 in PBMCs	Histone citrullination Histone acetylation in NogoA+ oligodendrocytes	↑ miR-17-5p, miR 326, miR 155	Le Dantec et al. (2015), Huynh and Casaccia (2010), Koch et al. (2013), Huynh and Casaccia (2013), van den Elsen et al. (2014), (Calabrese et al. 2014)
Type I Diabetes (DM1)	↓ DNMT1 in β cell Hypermethylation in ins1 gene	H3K9 dimethyaltion in CTLA4 genes	↑ miRNA-510,↓ miRNA-342 miRNA-191 in Treg	Miao et al. (2008), Al-Haddad et al. (2016)
Pulmonary diseases				
Chronic Obstructive Pulmonary Disease (COPD)	CpG hypermethylation of COX II, mtTFA, AHR genes	H3K4 trimethylation ↓HDAC activity H3S10 phosphorylation(leading to the activation of NF-kB regulated genes) Dysregulation of UPS	↓ miR-30, miR-146, miR-132, miR-155(leading to activation of NF-kB regulated genes) ↑ miR-199a-5p (leading to decrease in hypoxia-inducible factor 1-alpha)	Kabesch and Adcock (2012), Banerjee et al. (2012),Yao and Rahman (2012)
Asthma	Demethylation at promoter of IL-4and IFNG (a TH2 cytokine) in CD4+ T cells Hypermethylation at FOXP3 gene in Treg	↑ IL-13, FOXP3 histone acetylation ↑ Histone acetylation of Notch1 gene promoter (leading to T cell imbalance) in CD4+ T cell ↓ HDAC1, HDAC2	↑ miR-155,126, 21 and 19a (leading to an imbalance between TH1 and TH2) ↓ let-7 family (leading to ↑ IL-13)	Kabesch and Adcock (2012), Runyon et al. (2012), Bégin and Nadeau (2014), Yang and Schwartz (2012), Cui et al. (2013), Vercelli 2016
Pulmonary arterial hypertension (PAH)	Hypermethylation of SOD2 gene	↑ HDAC1, HDAC5	↑ miR-17, 21, 130, 145 ↓ miR-30c, 124, 193, 204, 206, 328, 424, 503	Archer et al. (2010), Peng et al. (2016), Samanta et al. (2016)
Cardiovascular diseases				
Hypertension (HTN)	Global hypomethylation Hypermethylation of promoter region of HSD11B2	–	↓ miR-9	Friso et al. (2008), Abi Khalil (2016)

Table 1 continued

Disease	Epigenetic dysregulation			References
	DNA methylation	Histone modification	Non-coding RNA	
Atherosclerosis	Global DNA hypermethylation Hypomethylation of chromosomal locus 14q32 Hypermethylation of MCT3 gene (leading to the modification of MCT) Hypermethylation of TFPI2	↑ Lysine deacetylase (KDAC)	↑ miR-233 s in PBMC	Zullo et al. (2014), Xiao et al. (2015), Zhu et al. (2005)
Ischemic heart disease (IHD)	Global DNA hypomethylation	↑ HDAC activity in histones 3 and 4	↓ miR-126, 17, 92a,145, 155 ↑ miR-133, miR-208a	Muka et al. (2016), Baccarelli et al. (2010)
Heart failure (HF)	Hypermethylation of LY75, ADORA2A genes	↑ HDAC1, 2	↓ miR-199b ↑ miR-1, 21, 24,377 ↑ lncRNA-LIPCAR	Kumarswamy et al. (2014), Samanta et al. (2016), Tao et al. (2016), Berezin (2016)
Atrial fibrillation (AF)	↑ DNMT1 Hypermethylation of homeobox gene Pitx2c, SUR2 Hypomethylation of SUR1	↓ H3K9 di and trimethylation ↑ HDAC6 (leading to disruption of the cardiomyocyte microtubule structure)	↓ miR-1, 26a, 26b, 133, 328, 590 ↑ miR-21, 146b ↑ miR206 (leading to repression of superoxide dismutase 1 (SOD1),↑ ROS) ↑ miR499 (leading to ↓SK3)	Tao et al. (2016), Martinez et al. (2015)
Gastrointestinal diseases				
Inflammatory bowel disease (IBD)	Hypermethylation of CHD-1 gene (leading to leakiness of the epithelial barrier and subsequent bacterial translocation and inflammation)	↓ HDAC3	↑ miR-16,23a, 29a, 106a, 107, 126, 191, 199a-5p, 200c, 362-3p and 532-3p	Ventham et al. (2013), Paraskevi et al. (2012)
Irritable bowel syndrome (IBS)	DNA methylation alteration	↑ Histone H4K12 acetylation	–	Kelly and Alenghat (2016)
Skin disorders				
Psoriasis	DR3	↑ HDAC-1 ↓ SIRT1 (NAD+-dependent deacetylase) leading to hyperproliferation of keratinocytes	↑ miR-146a, 125b, 203, 21	O'Rielly and Rahman (2015), Tung et al. (2015), Pollock et al. (2016)
Vitiligo	Global DNA hypermethylation (leading to T-cell infiltration of vitiligo skin) ↑ DNMT1 ↑(MBD1, MBD3, MBD4, MeCP2)	–	↑ miR-16,19b, 720	Shi et al. (2013), Zhao et al. (2010)
Bone and joint disorders				
Osteoarthritis (OA)	Hypomethylation of inflammatory related genes Hypermethylation of transcription factors involved in chondrogenesis	↑ HDAC1, HDAC2, HDAC7 (leading to ↓ extracellular matrix regulation genes, ↑ Extracellular matrix breakdown genes)	↓ miR-140 leading to ↓ chondrogenesi	Takahashi et al. (2015), Zhang and Wang (2015)

Table 1 continued

Disease	Epigenetic dysregulation			References
	DNA methylation	Histone modification	Non-coding RNA	
Osteoporosis	Hypermethylation of alkaline phosphatase and sclerostin genes (leading to MSC differentiation toward osteoclasts)	↓ Histone acetylation of H3,4 at the promoter region of osteocalcin (leading to ↓ bone mineralization) ↑ BET leading to osteoclast differentiation	↑ miR-204 and miR-433	Baud'huin et al. (2017), Huang et al. (2010), Kim et al. (2013), Fan et al. (2004), Zhang et al. (2011)
Neurological disorders				
Schizophrenia (SCZ)	↑ DNMT3a and DNMT1 (leading to ↓reelin and GABAergic dysfunction)	↓ H3K4me3 (leading to ↓ GAD1-glutamic acid decarboxylase-)	↑ miR-181b (leading to dysregulation of cortical gene expression)	Guidotti and Grayson (2011), Huang et al. (2007), Beveridge et al. (2008), Shorter and Miller (2015)
Major depressive disorder (MDD)	Hypermethylation of NR3C1 (gene encoding glucocorticoid receptor) Hypermethylation of BDNF promoter	↑ H3K14 and H4 acetylation in nucleus accumbens (NAc) ↑ H3K27me3 ↑ H3K4me3	↑ Let-7a-1, miR-376b, 208	Peña et al. (2014), Fass et al. (2014), Lolak et al. (2014)
Post-traumatic stress disorder (PTSD)	Global hypermethylation and differential methylation of genes associated with inflammation	↑ H3K27 methylation ↓ H3K9me2	↑ Let-7a-1, miR-376b, 208	Peña et al. (2014) Fass et al. (2014), Zannas et al. (2015), Sheerin et al. (2017)
Bipolar disorder (BPD)	Hypermathylation of KCNQ3 (encoding potassium voltage-gated channel) and HLA9 locus in brain ↑ DNMT3a and DNMT1 (leading to ↓ reelin and GABAergic dysfunction) Hypermethylation of BDNF promoter	↑ HDAC	↑miR-134, ↑ Let-7 family	Guidotti and Grayson (2011), Peña et al. (2014), D'Addario et al. (2012), Rong et al. (2011), Shinozaki et al. (2014)
Epilepsy	Hypermethylation of reelin promoter ↑ DNMT1 and DNMT3A	Histone H4 hypoacetylation of GluR2 promoter (glutamate2 receptor) hyperacetylation of BDNF ↑ HDAC2	↑ miR-124, 106b, 29a/b-1, 137, 181c, 15a, 26a, 212, 132 ↑ miR-128, 125b, 146a -132	Pulido Fontes et al. (2015), Kobow and Blumcke (2014)
Alzheimer's disease (AD)	↓ DNMT1 and MBD2 Hypermethylation of promoter of MTHFR gene Hypomethylation of promoter of APP gene Hypermethylation of APOE gene (leading to ↑ Aβ)	↑ HDAC6 (leading to tau phosphorylation and accumulation) ↑ H3S10 phosphorylation (leading to ↑ phosphorylated tau) ↑ H2AX phosphorylation (leading to DNA damage) ↑ H3K4me3 (leading to ↓ synaptic genes)	↓miR	Mastroeni et al. (2010) Balazs et al. (2011), Wang et al. (2013), Mastroeni et al. 2015
Parkinson's	↓ DNMT1 Hypermethylation of MAPT gene microtubule-associated protein tau Hypomethylation of Cyt P450 2E1gene	↓ H3 acetylation (inhibits gene expression, cell death) Hypoacetylation of PGCR-1α gene (leading to mitochondrial dysfunction) ↓ H3-K27me3	↓ miR-133b, 124 ↑ miR-132, 21, 224, 373	Feng et al. (2015), Jowaed et al. (2010), Ganai et al. (2016)

Table 1 continued

Disease	Epigenetic dysregulation			References
	DNA methylation	Histone modification	Non-coding RNA	
Huntington's	Hypermethylation of adenosine A2A receptor(A2AR)	↑ ESET (H3K9-specific methyl-transferase) subsequent ↓ genes leading to neuronal dysfunction ↑ H2AK119ubi↓ H2BK120ubi	↓ Multiple neural microRNAs	Milani and Fraenkel (2016), Buckley et al. (2010)
Polycystic ovary syndrome (PCOS)				
Polycystic ovary syndrome (PCOS)	Global DNA hypermethyaltion	↑ H3 and H4 acetylation (leading to androgen production)	↑ Let-7i-3 pm, miR-5706, 4463, 3665, and -638, 9, 18b, 32, 34c, and 135a ↓ miR-124-3p, 128, 29a-3p, let-7c	Yu et al. (2015), Ilie and Georgescu (2015), LaVoie (2005)
Type 2 diabetes				
Type 2 diabetes	Hypermehtylation of PDX1 gene leading to dysfunction in β cell differentiation Hypermethylation of PPARGC1A Hypermethylation of Superoxide dismutase (Sod2)	↓ H3K9me3 ↑ H4K20me3 of Sod2 promoter Histone hyperacetylation of IRS-1 and IRS-2 (leading to insulin resistance) ↑ H3K9, H3K23 and H4 acetylation	↑ miR-222, 375 ↓ miR-146	Al-Haddad et al. (2016), Ilie and Georgescu (2015), Guay et al. (2012)
Malignancies				
Malignancies	Global DNA hypomethylation Hypomethylation of retrotransposons (leading to increase genomic instability and activation of growth promoting genes) Site-specific hypermethylation (leading to ↓ tumor suppressor genes and DNA repair genes)	Global loss of acetylated H4-lysine 16 (H4K16ac) and H4-lysine 20 trimethylation (H4K20me3) ↑ HDACs ↑ H3K9 and H3K27 HMTs	↓ Tumor suppressor miRNAs ↑ Oncogenic miRNAs	Sharma et al. (2010), Shinjo and Kondo (2015)

CD4 cluster designation 4, *DNMT* DNA Methyltransferase, *H3K9* histone 4 lysine 9, *HDAC* histone deacetylase, *DR3* death receptor, *IL-6* interleukin 6, *FOXP3* forkhead box P3, *Treg* regulatory T cell, *PAD* peptidyl arginine deiminase, *PBMC* peripheral blood mononuclear cell, *CTLA-4* cytotoxic T lymphocyte Antigen-4, *COXII* Cytochrome-c Oxidase subunit II, *mtTFA* mitochondrial transcription factor A, *AHR* aryl hydrocarbon receptor, *H3S10* H3 at serine 10, *NF-kB* nuclear factor-Kappa B, *IL4* interleukin-4, *IFNG* interferon-gamma, *TH2* T Helper 2, *SOD* superoxide dismutase, *HSD11B2* Hydroxy-Steroid (11-beta) Dehydrogenase 2, *KDAC* lysine deacetylase of histone protein, *MCT* monoCarboxylate transporter, *LY75* lymphocyte antigen 75, *ADORA2A* adenosine receptor A2A, *SUR* sulfonylurea receptors, *ROS* reactive oxygen species, *SK3* calcium-activated potassium channel 3, *CHD-1* Chromodomain-Helicase-DNA-binding protein 1, *H4K12* histone H4 at lysine 12, *SIRT1* sirtuin 1, *NAD* nicotinamide adenine dinucleotide, *MBD* methyl-DNA-binding domain protein, *MeCP2* methyl-CpG-binding protein 2, *MMP* matrix metallo-proteinase, *MSC* mesenchymal stem cell, *BET* bromodomain and extra-terminal family, *GABA* gamma amino butyric acid, *NAc* nucleus accumbens, *BDNF* brain-derived neurotrophic factor, *GluR2* glutamate2 receptor, *MTHFR* methylene tetra hydro folate reductase gene, *APP* amyloid precursor protein, *APOE* apolipoprotein E, *Aβ* amyloid beta, *MAPT* microtubule-associated protein tau, *Cyp450* cytochrome p 450, *PGC-1α or PPARGC1A* peroxisome proliferator-activated receptor gamma co-activator 1-alpha, *H2A119ubi* ubiquitination of histone H2A on lysine 119, *PDX1* pancreatic and duodenal homeobox 1, *IRS* insulin receptor substrate, *H4K16ac* acetylated H4-lysine 16, *H4K20me3* H4-lysine 20 trimethylation, *HMT* histone methyl transferase

that hypomethylation of retrotransposons, the key regulator of gene expression occur in the early stage of tumorigenesis involved in chromosome instability. In contrast to genome hypomethylation, the essential role of hypermethylation and silencing of the promoter region of tumor suppressor genes, transcription factors, and DNA repair genes has been well recognized in carcinogenesis (Sharma et al. 2010).

Changes in histone epigenetic marks have been implicated in varied forms of cancer. Changes in H3K27m3 and H3K9me3 pattern are associated with aberrant gene suppressions. The underlying mechanisms of histone epigenetic modifications were attributed to the changes in the expression of epigenetic enzymes such as HATs, HMTs, HDACs and histone demethylase (HDMs). Importantly, overexpression of EZH2, H3K27 methyltransferase was identified in breast and prostate cancer that were associated with poor prognosis (Sharma et al. 2010). The levels of HDACs were shown to be changed significantly in various types of cancers including hematological malignancies. MicRNAs are another key player that their dysregulation involves in the progression of carcinogenesis. They have a potential dual function as oncogenes and oncosuppressor gene. While the expression of oncogenic miRNA increased in cancerous lesion, the level of tumor suppressor miRNA was shown to reduce (Iorio and Croce 2012).

Environmental toxicants induce epigenetic toxicity

There is a close association between environmental toxicants and epigenetic alterations. A variety of epidemiological and experimental studies on animal, human and in vitro models have shown the influence of environmental toxicants on epigenetic regulations and their implementation on development, health and disease risk (Mensor et al. 2001). Although the toxicant-induced epigenetic alterations are minor, they could possibly be accumulated to the toxic level and exert irreversible effects on human health or even next generations. Up until now, a variety of environmental toxicants have been identified for their role in aberrant epigenetic modifications such as DNA methylation, histone modifications, and microRNA expression. Still, there are a large number of chemicals remain to be examined for their epigenetic toxicity (Littell et al. 2002). As the scope of these topics has expanded vastly, here we have focused on selected number of toxicants with known epigenomic effects and their association with diseases (Table 2).

Metals

Heavy metals are the most widespread contamination in the ecosystems. Different heavy metals such as Cadmium (Cd), Mercury (Hg), Arsenic (As), Chromium have been well recognized for their role in epigenetic modulations (Perez et al. 1990; Kandil et al. 1994). There are various available studies which reveal the linkage between environmental metals and DNA methylation. The underlying mechanisms of their epigenetic malregulations is mostly related to increase oxidative stress via the generation of reactive oxygen species (ROS) and induction of DNA damage that further inhibits the capacity of methyltranferases to interact with the DNA and hence causing an overall modified methylation of the cytosine at CpG sites (Wang et al. 2012; Tong et al. 2013).

Cadmium

Cadmium is a well-known carcinogenic metal with low mutagenic potency. Different possible mechanisms have been identified regarding carcinogenesis of the cadmium. Among them, the generation of ROS and aberrant alteration of DNA methylation pattern play a major biological role (Onishchenko et al. 2008). Recent studies have shown that based on the doses and duration of exposure, cadmium could induce hypomethylation or hypermethylation through modulating methyltransferase activity. Exposure to high dose or acute low dose of cadmium inhibits DNMT activity and therefore decreases DNA methylation states of particular genes, while prolonged, low doses induce DNMT activity and increase DNA methylation of gene associated with cell transformation (Benbrahim-Tallaa et al. 2007). Accordingly, it was shown that low dose of Cd induces hypermethylation of caspase-8 CGI in mice liver after 48-week exposure (Wang et al. 2012).

Arsenic

Arsenic is a well-known established carcinogen that can be found in two forms of organic and inorganic in the environment. Binding of arsenic to elements such as oxygen, sulfur or chlorine forms inorganic arsenic while combining to carbon elements forms organic arsenic. When absorbed to the body, the arsenic with inorganic nature is readily methylated for detoxification with the help of enzymes using S-adenosyl methionine (SAM) in the reaction. The fact that DNA methyltranferases also need SAM as a donor of the methyl group suggested a role for the DNA methylation in the carcinogenicity of arsenic (Okoji et al. 2002). It is also noted that SAM depletion as a result of arsenic metabolism could affect the activity of other methyltransferases such as histone methyltransferase. Moreover, various studies have shown that arsenic toxicity is associated with genomic hypermethylation as well as global hypo and hypermethylation. There are also sparse studies on modulation of histone acetylation, phosphorylation and miRNA expression after arsenic exposure (Okoji et al. 2002; Ren et al. 2011).

Table 2 Environmentally induced epigenetic toxicity in rodent models

Environmental exposure	Species	Exposure	Stage	Effects	Epigenetic change	References
Bisphenol A	Mouse	Maternal	In utero	Reproductive, neurological and metabolic	↓ DNA methylation of Igf2r and Peg3 genes	Chao et al. (2012)
Formaldehyde	Rat	Adulthood	Adulthood	Behavioral abnormalities	↓ DNA methylation of reelin gene	Levenson et al. (2006)
Cadmium	Rat, mouse	Adolescence	Later adulthood	Hepatic abnormalities	↑ Caspase-8 CGI DNA methylation	Wang et al. (2012)
Nickel	Rat, mouse	Early adulthood	Later adulthood	Tumors	↑ miR-222 (↑expression of CDKN1B and CDKN1C), ↓miR-203, ↑ miR-152 ↑ Histone demethylation ↓ Histone H4 acetylation ↑ Histone ubiquitination	Chen et al. (2006), Zhang et al. (2013)
Methyl mercury	Mouse	Neonatal	Adulthood	Behavioral abnormalities	↑ H3 methylation ↓ H3 acetylation (promoter IV)	Onishchenko et al. (2008)
Dibutylphthalate (DBP)	Rat	In utero	In utero to adulthood	Decreased testicular testosterone	Histone modifications	Schubert (2014)
2,3,7,8-Tetrachlorodibenzop-dioxin (TCDD)	Mouse	In utero	In utero to adulthood	Mammary and hepatic abnormalities	↑ CpG methylation of the BRCA-1 promoter	Papoutsis et al. (2015)
Urethane	Mouse	Late childhood	Adulthood	Hepatic tumors	↑ H3 di, trimethylation (H3K27me3) ↓ miR-138	Pandey et al. (2014)
Vinyl carbamate	Mouse	Adolescence	Adulthood	Pulmonary carcinogenesis	Altered miRNAs expression	Kassie et al. (2010)
Alcohol	Rat	In utero	In utero	Neurological behavior	Altered miRNAs expression	Ignacio et al. (2014)
Caffeine	Mouse	In utero	Early adulthood	Early adulthood cardiac abnormalities	Altered DNA methylation patterns in A1AR +/+	Buscariollo et al. (2014)
Arsenic	Mouse	In utero	In utero	Reproductive, neurological, behavioral, metabolic	DNA Hypomethylation and hypermethylation Altered miRNAs expression Histone modification	Okoji et al. (2002), Ren et al. (2011)

BRCA-1 breast cancer, *Peg3* paternally expressed gene 3, *Igf2r* insulin-like growth factor 2

Nickel

The mechanism of nickel-induced carcinogenicity and cardiotoxicity is still not clear. It has been suggested that nickel causes the replacement of magnesium in DNA interactions, stabilizing the condensation of chromatin and initiates de novo DNA methylation (Baccarelli and Bollati 2009). It is evident from various studies that nickel could also alter gene expression through histone modifications (Ke et al. 2006). Upon in vitro exposure to soluble $NiCl_2$, a marked reduction in the global H4 acetylation as well as increase in H3 methylation were detected (Chen et al. 2006). Furthermore, exposure to nickel ion increased H3 methylation of particular gene including *gpt* transgene involved in induction of gene expression (Chen et al. 2006). Changes in different miRNAs have also been implicated in nickel-induced tumorigenicity (Zhang et al. 2013; He et al. 2014).

Chromium

There are a variety of genetic mutations in the lung cancer that were associated with chromium exposure; however, not much is known about the exact mechanism of chromium-induced epigenetic changes. It has been investigated that chromate exposure accelerates p16 hypermethylation, leading to p16 silencing in tissues obtained from the lungs affected with cancer (Kondo et al. 2006). Chromium also

reduces the in vitro H3 phosphorylation and methylation along with the H3 and H4 acetylation (Schnekenburger et al. 2007). Study on 20 lung carcinomas and 13 squamous lung carcinomas showed a significant decrease in miR-143/145 expression of nearly 80% of the patients (He et al. 2013).

Methyl mercury

Methyl mercury is a toxic environmental pollutant with neurotoxic effect that is present in high amount in the sea foods. In vivo studies on mice model have confirmed that prenatal exposure to methyl mercury causes serious learning and motivational changes in offspring. Accordingly, chronically prenatal exposure to methyl mercury induced three types of epigenetic alterations including DNA hypermethylation, decreased H3 acetylation of brain-derived neurotrophic factor promoter and increased histone H3 methylation (Ceccatelli et al. 2013). Also, it was shown that developmental exposure to low level of the methyl mercury initiates epigenetic alterations in the hippocampus region (Onishchenko et al. 2008).

Trichloroethylene (TCE), dichloroacetic acid (DCA), and trichloroacetic acid (TCA)

TCE and its metabolites are the environmental toxicants which induce peroxisome proliferation and are carcinogenic in nature. In vivo studies on mice models have shown that these toxicants reduce methylation of the promoter regions of the proto-oncogenes c-jun and c-myc. It was further evident that TCE-induced hypomethylation of proto-oncogenes was mostly related to the depletion of SAM, the methyl donor for DNMTs (Baccarelli and Bollati 2009). In fact, studies on the effect of TCE metabolites on other epigenetic markers are very limited.

Air pollution

Air pollution, especially the particulate matter (PM), is a well-established risk factor for various types of diseases such as cardiovascular disorders and lung cancer (Brook et al. 2004). A recent study on steel plant workers blood samples showed decreased global DNA methylation in LINE-1 and Alu (Tarantini et al. 2009). In a similar study, it was confirmed that PM exposure is closely associated with the diminished DNA methylation of inducible nitric oxide synthase gene (iNOS), involved in ROS production (Tarantini et al. 2009). Moreover, decrease in H3K4 dimethylation, H3K9 acetylation and mRNA22 expression was also reported in the leukocyte of steel worker exposed to metal-rich air PM (Hou et al. 2011).

Benzene

Benzene as the widely used chemical in industrial products has been associated with different hematological malignancies and endocrine disruptions (Bahadar et al. 2015). There are a number of studies on epigenotoxicity of benzene that are mostly focused on DNA methylation and therefore less is known about other epigenetic effects of this chemical on human health. It was shown that low-level exposure to benzene induces global hypomethylation in the peripheral blood of gas station workers and traffic wardens and as the risk factor of acute myelogenous leukemia. Similarly, exposure to the higher level of airborne benzene was related to hypermethylation of p15 and poly (ADP-ribose) polymerases-1 (PARP-1), also hypomethylation of melanoma antigen-1 (MAGE-1) gene promoter (Hou et al. 2011).

Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)

RDX is among the common environmental pollutants produced as a result of military and civilian activities. Exposure to RDX was associated with neurotoxicity and malignancies (Jenkins et al. 2006). A recent study on a mouce model has revealed the aberrant expression of different miRNAs after long-term exposure to RDX (Zhang and Pan 2009). Based on the tissue type, a significant increase in the expression of oncogenic miRNAs and decreased in tumor-suppressing miRNAs were reported (Zhang and Pan 2009).

Epigenetic drugs and their applications

As discussed before, environmental toxicants can induce epigenetic changes result in a variety of diseases. Finding the causal associations between epigenetic modifications and particular diseases has offered the new therapeutic targets. Indeed epigenetic therapy has recently emerged as an important pharmaceutical approach (Fig. 2). So far, different epigenetic inhibitors as well as microRNA-based modulators have been introduced that can reduce or abolish epigenetic enzyme activity in vitro. While many are at pre-clinical or clinical phase, there are few epigenetic drugs that have approved clinical use.

DNA methylation inhibitors (DNMTi)

Several nucleoside-like drugs that function as methylation inhibitors and potential tumor suppressors have been approved to use in the clinic. Azacitidine is the analog of cytidine that become incorporated into DNA during replication process and could exert its antineoplastic effect through inhibition of DNA methylation (Kaminskas et al. 2005).

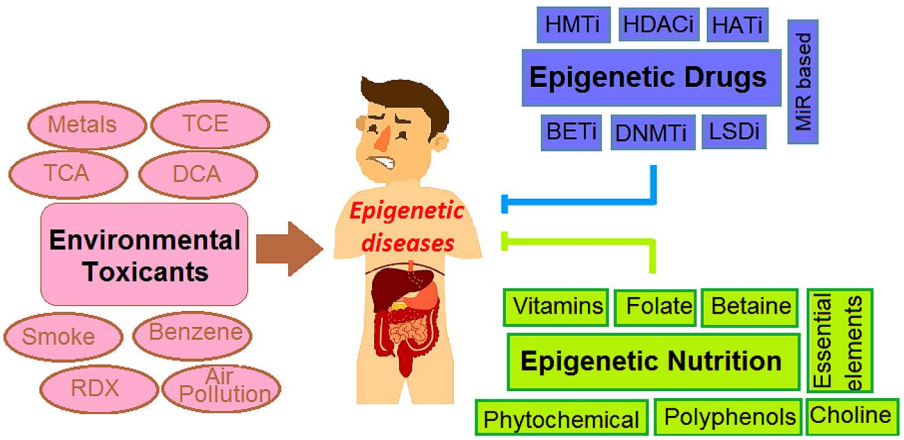

Fig. 2 Epigenetic alterations induced by environmental factors and its reversal approaches. *HMTi* histone methyltransferase inhibitor, *HDACi* histone demethylase inhibitor, *HATi* histone acetyltransferase, *BETi* bromodomain and extraterminal domain inhibitors, *DNMTi* DNA methylation inhibitors, *LSDi* lysine-specific demethylase inhibitor, *TCE* trichloroethylene, *TCA* trichloroacetic acid, *DCA* dichloroacetate, *RDX* hexahydro-1, 3, 5-trinitro-1, 3, 5-triazine

When azacitidine is recognized by DNMT1, an irreversible DNMT1–azacitidine conjugation is formed leading to breakdown of responsible enzyme and reduction of methylation process (Santi et al. 1984; Momparler 2005). Though azacitidine was approved for myelodysplastic syndrome (MDS) treatment, still possible improvements are needed to increase its stability and reduce toxic side effects. Decitabine, 5-aza-2′-deoxycytidine, is another FDA-approved hypomethylating agent with almost similar therapeutic effect on MDS patients.

Zebularine, a cytidine analog has demonstrated the similar mechanism of assimilating into DNA and creating a covalent bond with DNMT1. The clinical trial is underway, as this isoform showed remarkable results in mouse models (Cheng et al. 2003).

The DNMT inhibitors are not limited to the nucleoside analogues. RG-108, the analogues of *N*-phthaloyl-L-tryptophan, is a small molecule that directly binds to DNMT1 binding sites and blocks the enzyme. Based on in vitro studies, it was shown that RG-108 treatment significantly reduces the global DNA methylation and slows down tumor cell growth in human cancer cell lines (Brueckner et al. 2005). The low toxicity and high specificity of RG-108 make it an attractive potential remedy in the upcoming years. MG98 is a 20-base pair oligonucleotide having capability to conjugate with 3´ un-translated part of DNMT1 mRNA and blocking gene transcription (Amato 2007). Although there are controversies over the tumor type sensitivity and effective dose of MG-98, it has exhibited significant anti-tumor activity with lower toxicity in the clinic (Winquist et al. 2006).

Bromodomain inhibitors (BETi)

Bromodomain and extra-terminal motif protein (BET) are the group of protein containing bromodomain that recognize acetyl group of histones, and were associated with transcriptional elongation of acetylated chromatin (Dawson et al. 2012). BRD4, a well-studied member of BET family, has essential role in cell mitosis and maintenance of chromatin architecture (Maruyama et al. 2002; Jang et al. 2005). BRD4 was also shown to bind to the promoter regions of particular oncogene and mediate gene transcription. Moreover, the fusion of BRD4 with nuclear protein in testis (NUT) plays key role in oncogenesis and tumor growth promotion in NUT midline carcinoma (French et al. 2008).

The distinctive functionality and specificity of BET protein make them a potential target for anti-cancer therapeutic interventions. Accordingly, the bromo-domain inhibitor JQ-1 has shown a promising result in multiple myeloma, a myc-dependent tumor in the mouse model. JQ-1 binds competitively to the BRD4 and involves in the displacement of BRD4 fusion oncoprotein from chromatin that finally leads to cell apoptosis and tumor suppression (Mertz et al. 2011). However, due to its short half-life, JQ-1 is not applied in human clinical trial. I-BET-726 is a BET inhibitor with similar functionality that controls expression of Bcl2, the key anti-apoptotic factor. This inhibitor had shown to prevent the development of neuroblastoma cancer (Wyce et al. 2013). Other BET inhibitors include BET151/762, PF-1, RVX-208, BMS-986158, OTX015, and PLX-51107 that are under developmental investigation for clinical use in human medicine (Wadhwa and Nicolaides 2016).

Histone acetyltransferase inhibitors (HATi)

Different HATis could inhibit the catalytic activity of histone acetyltransferases either in selective or non-selective manner and were shown to have potential therapeutic properties for treatment of many diseases. Current researches are focused mainly on two classes of HATis including

synthetic small molecules and bi-substrate inhibitors. Lys-CoA peptide, a potent selective bisubstrate inhibitor of p300 and p300-dependent transcriptional activation, was shown to become activated only when it is used in conjugation with intermediate cytotoxic detergents and/or via microinjection. The new promising 300/CREB-binding (CBP) inhibitor named C-646 binds with high selectivity to the druggable pocket of p300 and behaves as a cofactor competitor (Balasubramanyam et al. 2003). Studies have shown that C-646 could suppress the cell survival and invasion of prostates tumor cells (Santer et al. 2011).

Low potency, instability and antioxidant activity of HATi are among the factors that limited the therapeutic functionality of this groups of epigenetic modulators (Wapenaar and Dekker 2016).

Histone methyltransferase inhibitors (HMTi)

HMTi is another epigenetic modulator, acting through deactivation of different HMTs. Taken into consideration the important roles of EZH2 and DOT1L in cell function, recent attempts are mostly focused on discovering the specific EZH2 and DOT1L inhibitors for the treatment of disease conditions (Morera et al. 2016). Deazaneplanocin-A, a well-studied EZH2 inhibitor, showed high selectivity towards prevention of trimethylation of lysine-27 and lysine-20 on histone H-3 and H-4, respectively. The compound showed profound apoptotic effects on various cancer cells, such as liver, lung, brain, breast and prostate. However, due to the low specificity of deazaneplanocin-A, it has not yet entered clinical uses. EPZ-5676 is a potent and selective DOT1L inhibitor acting as S-adenosyl methionine (SAM) competitor shown to induce tumor regression in the mouse model of MLL-rearranged leukemia. EPZ-5676 has currently entered the first phase of the clinical trial for leukemia (Stein et al. 2015).

Lysine demethylase inhibitors (LSDi)

Histone demethylase is classified into two main groups, including the lysine-specific demethylases 1 and 2 (LSD1/2) and Jumonji domain-containing proteins. Given the important role of histone demethylases in cancer proliferation and inhibition of tumor suppressor gene as well as a modulator of stress-evoked transcription in mental retardation, many researches have focused on targeting these epigenetic modulators for treatment of related diseases (Morera et al. 2016; Rusconi et al. 2016).

Tranylcypromine and phenelzine are the approved LSD1 inhibitors that were primarily considered as anti-depressant agents. Currently, many attentions have pointed towards the application of tranylcypromine and its derivatives in cancer treatment (Morera et al. 2016). While different subfamilies of JMJC demethylases were identified for their anti-proliferative activity, the limited cell permeability and low selectivity are the major challenges to the clinical use of these compounds.

HDAC inhibitors (HDACi)

HDAC inhibitors are among the most promising epigenetic therapies that act with high specificity against HDACs. Based on their structure, HDACi is classified into four groups including hydroxamic acids, benzamides, epoxyketone-containing cyclic tetrapeptides and short-chain fatty acid (Dokmanovic et al. 2007).

Class I and II of HDAC proteins could be targeted by hydroxamic acid inhibitors, which have potency for tumors treatment. Trichostatin-A and Vorinostat are the first approved hydroxamic acid inhibitors for the advanced, persistent and concurrent T-cell lymphoma (Mann et al. 2007). Vorinostat triggers hyperacetylation of histones along with non-histones proteins such as p53 and heat shock protein-90 that lead to apoptosis and cell death. Vorinostat has shown to be a fascinating nominee for combination therapy using non-epigenetic and epigenetic treatments (Richon 2006). The HDAC inhibitor, trichostatin-A, has a marked improvement in the induced pluripotent stem cells stimulation, and enhancement of cardiac transcriptional factors, which play a vital role in the transformation of stem cells into endothelial cells and cardiomyocytes. Other approved hydroxamic acid inhibitors are panobinostat and belinostat that could suppress the activity of all types of HDACs and are indicated for lymphoma and leukemia patients. Among studied benzamides HDACi, entinostat is a potent therapeutic compound that acts selectively against two classes of HDACs: I and IV. Meanwhile, it is undergoing phase 2 of clinical studies for treatment of refractory and relapsed Hodgkin lymphoma. Mocetinostat is an approved benzamides HDACi with selective activity for the treatment of myelodysplastic syndrome. Romidepsin is a cyclic tetrapeptides antibiotic with antineoplastic activity via inhibition of HDAC I and II (Lemoine and Younes 2010). In 2009, romidepsin was approved for the treatment of cutaneous T-cell lymphoma patients after receiving systemic therapy.

Up to date, the combination of anti-cancer and epigenetics drugs has attracted a great research attention in cancer therapy. Increased specificity and reduced toxic effects as well as overcoming drug resistance, are the emerging advantages of the combination therapy over monotherapy. HDAC inhibitors are also involved in demethylation of silent tumor suppressor genes via down-regulation of DNMT-1, thus suggesting a synergistic effect of HDACi and DNMT inhibitor combination. Based on clinical research on patients with recurrent metastatic NSCLC,

use of azacitidine and entinostat demonstrated profound decrease in hypermethylation of genes, promoter regions and showed enhanced antitumor activity (Vendetti et al. 2015).

MicroRNA-based therapeutic

Targeting non-coding RNAs associated with the epigenetic regulations is another promising strategy for treatment of a variety of diseases caused by epigenetic modifications (Panzeri et al. 2016). As previously described, non-coding RNAs are divided into two main groups: microRNA and long non-coding RNA. Compared to lncRNAs, we now have a much better understanding of biological roles of miRNA. Due to their small size, genetic targeting of this class of non-coding RNA is possible. Currently, two major types of miRNA-based therapy exist including individual miRNA mimics and inhibitors (anti-miRs) that modulate the pathological conditions by increasing or silencing the specific miRNA expressions, respectively (Schmidt 2014). The antisense strand of miRNA mimic is identical to the sequence of target miRNA, thus, binds to the RNA-induced silencing complex (RISC) and regulates the expression of the target gene (Kasinski et al. 2015). In contrast, inhibition of an overexpressed miRNA can be achieved using anti-miRNA oligonucleotide (AMO). AMOs are synthetic reverse complements that could bind and inactivate targeted miRNA through various mechanisms (Lennox and Behlke 2011). Up to date, three miRNA-based therapeutics have entered clinical trials named miravirsen, RG-101, and MRX34. Miravirsen an anti-sense oligonucleotide that targeting miR-122 was the first drug for treatment of hepatitis C virus infection (HCV) (Gebert et al. 2014). The anti-miR-122 compound RG-101 is an *N*-acetyl D-galactosamine (GalNAc)-conjugated anti-miR-122 which is currently in phase II clinical trials (Baek et al. 2014). MRX34 is a miR-34a mimic-loaded liposomal nanoparticle with exploiting tumor suppressing the function of miR-34 for the treatment of cancer (Cortez et al. 2015).

Like other gene-based therapeutics, miRNA mimics and AMOs are susceptible to nuclease degradation and reticuloendothelial system clearance (Chen et al. 2015b). Thus, an efficient gene delivery strategy will be needed. To date, huge studies have been conducted to improve the stability of miRNA-based therapeutics and transport them efficiently to the target cells. Chemical modifications of targeting oligonucleotide such as 2′-deoxy oligonucleotides, 2′-O-methyl–modified oligoribonucleotides (2′-OMes), cholesterol moiety–conjugated 2′-OMe (antagomiR) (Krützfeldt et al. 2005), locked nucleic acid (LNA) (Elmén et al. 2008), peptide nucleic acids (PNA) (Fabani et al. 2010), oligonucleotides containing 2′-O-methoxyethyl (2′-MOE), 2′-flouro (2′-F), and phosphorothioate (PS) backbone modifications have been employed to increase the nucleic acid resistance against nucleases (Lennox and Behlke 2011). Another approach for miRNA-based gene delivery is exploiting the physical force like ultrasound and microinjection to instantaneously disrupt the integrity of cell membrane and facilitate the gene transfection (Joo et al. 2014; Kwekkeboom et al. 2015). Besides, biological and chemical vectors are getting much attention because of their potential capacity to deliver the transgene in a secure way. Viral vectors containing the sequence of a mature miRNA and providing its expression in target cell have revealed high transfection efficiency in some reports (Pfeffer et al. 2004; Miyazaki et al. 2012). The other biological vector example worth mentioning is exosome. Exosomes are one of the subsets of extracellular vesicles whose function is the intracellular transport of genetic materials; therefore, they may be a good candidate for exogenous oligonucleotides delivery to target cells (Momen-Heravi et al. 2014; Emanueli et al. 2015; Gambari 2015). Various chemical gene delivery vehicles including lipids (Trang et al. 2011; McLendon et al. 2015), polymers (Chien et al. 2015; Louw et al. 2016; Tu et al. 2017), carbon nanotubes (Masotti et al. 2016) and inorganic nanoparticles (Crew et al. 2011) have be en designed with the purpose of transfection efficiency enhancement.

Despite the recent discoveries in miRNAs biological roles and progresses in miRNA-based therapy, more understanding and elucidating potentiality of miRNAs is still needed for development of new miRNA-based therapeutics. In fact, it is expected that miRNA-based therapeutics will be one of the major classes of therapeutic molecules in the near future.

Nutrition and toxicant-induced epigenetic alterations

Cumulative studies have indicated that epigenetic machinery is sensitive to human lifestyle factors such as diet, social status, stress, etc. (Choi and Friso 2010). Indeed there are widely scattered reports on epigenetic effects of dietary components (nutrients, metabolites, and bioactive food compounds) and their possible role in the reversal of abnormal epigenetic marks (Aggarwal et al. 2015) (Fig. 2). Therefore, finding strategies that use dietary factors for targeting epigenetic modifications could be an alternative method for treating epigenetic pathophysiological conditions including cancer, aging, Alzheimer's, and brain, cardiometabolic, immune, metabolic, and neurodegenerative diseases.

Different dietary compounds including micro- and macronutrients including methyl donors (folate, choline, and various vitamins) and phytochemicals (such as

thiosulfonates, polyphenols, glucosinolates, or terpenoids) have shown to be able to affect epigenetic mechanisms (Prebet and Gore 2015). Various dietary methyl donors participate in one-carbon metabolism and change DNA methylation through methionine pathways by regulating the level of co-substrates S-adenosyl methionine (SAM) and methyltransferase inhibitor S-adenosyl-homocysteine (SAH) (Park et al. 2012). Folate and its partners, vitamin B_6, and B_{12} are the most important methyl donors. In case of folate deficiency, choline, betaine, and methionine are critical for maintenance of adequate SAM levels and thus to assure adequate methylation (Prebet and Gore 2015).

Other chemopreventive resources for epigenetic alterations are the dietary polyphenols including curcumin, genistein, epigallocatechin gallate (EGCG), resveratrol, sulforaphane, and equol. These bioactive compounds are commonly found in green tea, vegetables, fruits and red wine. Different studies have shown that polyphenols mediated the reversal of abnormal epigenetic alterations and, therefore, can change abnormal gene expression (Aggarwal et al. 2015). The chemopreventative potential of these compounds is attributed to their ability to inhibit DNMT as well as their ability to catalyze histone modifications. Relatively, it was shown that curcumin inhibits HAT activity whereas resveratrol, sulforaphane, and butyrate inhibit HDAC, and therefore influence the expression of specific genes (Choi and Friso 2010).

Water-soluble B vitamin, biotin, niacin and pantothenic acid are well studied for their epigenomic reversal activity. For example, biotin is a substrate for histone biotinylation and niacin for histone ADP-ribosylation (Remely et al. 2015). Vitamin D_3 can be utilized as an epigenetic therapy for cancers at early-stage based on its chemoprevention roles in demethylation and upregulation of tumor suppressor genes (Stefanska et al. 2010). Also, studies have shown that vitamin A could affect histone methylation of genes involved in the production of several cytokines and thus changes the cytokines responses (Arts et al. 2015).

Although essential elements (selenium, zinc manganese copper, etc.) have long been investigated for their anticancer properties, their key regulatory role in changing abnormal epigenetic marks is being emerged. Different studies have shown that selenium reduces DNA methylation potential by altering SAM and S-adenosylhomocysteine concentrations, the key intermediate metabolites of regulatory one-carbon methylation pathway (Redman et al. 1998; Uthus et al. 2006). Zinc is the cofactor of several enzymes involved in the methionine pathway. Its deficiency decreased SAM turnover, therefore affecting methylation of both DNA and histones (Wallwork and Duerre 1985).

It is widely believed that epigenetic modifications are the key controller of cell fates during early embryonic and primordial cell development. Environmental exposure in utero highly influences the epigenetic patterns of offspring resulting in alterations of gene expression and implementation of different pathophysiological conditions. Furthermore, one can agree that embryonic period is the time that environmental toxicants could exert their influence in high level to change epigenetic normal pattern (Rezvanfar et al. 2016). In this regards, natural chemoprotective compounds could be applied as important protective agents against environmental epigenetic modulators. Moreover, nutrition has a major protective impact on the epigenome of the adult during early adolescent and gestation period (Chango and Pogribny 2015).

Conclusion

Based on the emerging key regulatory role of epigenetic modulation in the etiology of pathophysiological conditions, it is likely that epigenetic area will become the focus of future biological and pharmaceutical research. Still, more attempts are needed to discover the underlying mechanisms of gene-specific epigenetic modifications and their association with particular malignancies. Considering the important role of epigenetic abnormalities in the etiology of many diseases, investigating the epigenotoxic impact of chemicals is of high priority to human health. Therefore, a shift towards more concentrated epigenetic research is required for evaluation of chemical toxicity. At the time being, few epigenetic drugs are available in the market, and many are in the preclinical and clinical trial phases. Besides pharmaceutical approaches, there is growing body of evidence that epigenetically active food compounds play a protective role in the regulation of pathological progressions and could be considered as a potential alternative for epigenetic therapy. In this regard, nutritional research and policies have initiated to provide guidelines for sufficient daily intake of nutrients and prevent nutritional deficiencies.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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