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Effect of Environmental Chemical Exposures on Epigenetics of Diseases: A Systematic Review

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ABSTRACT- Every year more than 13 million deaths worldwide are due to environmental pollutants, and approximately 24% of diseases are caused by environmental exposures that might be averted through preventive measures. Out of all these environmental chemicals, effects of air pollution is responsible for death of 3.3 million people prematurely worldwide - a figure that could double by 2050 if emissions continue to rise at the current rate. Increasing number of evidences has linked environmental pollutants with epigenetic variations, including changes in DNA methylation status, histone modifications and other factors like incorporation of miRNAs, nucleosome remodeling, etc. These entire mechanisms are likely to play important roles in disease aetiology, and their modifications, thus providing further understanding of disease aetiology, as well as biomarkers for these exposures to environmental chemicals and/or prediction of the risk for the disease. In this, we had tried to summarize the different epigenetic alterations related to environmental chemical exposures, and propose the probable mechanisms of action behind such epigenetic changes. We will also focus onopportunities, challenges and further directions for future epidemiology research in environmental epigenomics. Further studies are needed in this regard to solve methodological and practical challenges, including uncertainties about stability over time of epigenomic changes induced by the environment, tissue specificity of epigenetic alterations, validation of laboratory methods, and adaptation of bioinformatic and biostatistical methods to high-throughput epigenomics. Moreover, there are several reports of epigenetic modifications arising from environmental chemical exposures, but most have not been directly linked to disease endpoints.

Key-words- Environmental chemicals, Epigenetics, Disease susceptibility

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INTRODUCTION

Being a part of our daily life, chemicals in the day to day use may also cause different diseases through various mechanisms. Environmental pollutants results inapproximately 13 million deaths approximately every year and as much as 24% of the diseases are estimated to be caused by environmental exposures that can be prevented (Pru¨ss-U¨stu¨n Annette, 2006).Out of all these environmental chemicals, effects of air pollution is responsible for death of 3.3 million people prematurely worldwide - a figure that could double by 2050 if emissions continue to rise at the current rate (Lelieveld *et al*., 2015).

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Growing evidence suggests that environmental pollutants may cause diseases via epigenetic mechanism-regulated gene expression changes (Tang *et al*., 2007; Bezek*et al*., 2008). Continuous exposure to many chemicals, including through air, water, food or other media and products resulting in various diseases and health impacts are well assessed, however very little is known about the mechanism at the epigenetic level. This review has tried to summarize the effect of different environmental chemical exposures on epigenetics of various diseases studied till now (Table 1).

Epigenetics-Linking Factor between Environment and different diseases

Epigenetics defined as heritable changes in gene function occuring without a change in the nucleotide sequence (Bird, 2007). These changes in phenotypic traits occur due to variety of mechanisms (Fradin and Bougneres, 2011). An Epigenetic factor that regulates gene expression mostly includes DNA methylations, histone modifications, and expression of microRNAs (miRNAs) (Reik *et al*., 2001; Grewal and Moazed, 2003). An epigenetic mechanism that modifies chromatin structure can be classified into four main categories: DNA methylation, covalent histone

modifications, and non-covalent mechanisms like incorporation of histone variants and nucleosome remodeling and non-coding RNAs including microRNAs (miRNAs).

Epigenetic Changes due to environmental chemical exposures

Changes in these epigenetic factors have been shown to be induced by the exposure to various environmental chemicals linked with different diseases (Baccarelli *et al.*, 2009; Heightman *et al*., 2011; Wright, 2011).Entire list of such epigenetic changes as described by Hou, Zhang, Wang and Baccarelli due to different environmental factors like pollution, chemicals, pesticides, etc are enlisted in Table 1. Various epigenetic mechanisms responsible for it are described below as follows-

DNA Methylation

Out of all, DNA methylation is the mostthoroughly studied epigenetic modification in mammals, playing an important role in regulating gene expression and chromatin architecture, in association with histone modifications and other chromatin associated proteins. DNA methylation mainly occurs by the covalent modification of cytosine residues in CpG dinucleotides in mammals. In human genome, CpG dinucleotides are not evenly distributed across the human genome but are instead concentrated in 'CpG islands' and regions of large repetitive sequences (e.g. centromeric repeats, retrotransposon elements, rDNA etc.) (Bird, 2002; Takai *et al*., 2002).

During development and in differentiated tissues, most of the CpG sites in the genome are methylated, but the mostof the CpG islands usually remain unmethylated also (Suzuki *et al.*, 2008). However, some CpG island promoters get methylated during development, resulting in long-term transcriptional silencing (Bird, 2002). DNA methylation uses various mechanisms to heritably silence genes and non-coding genomic regions. DNA methylation can lead to gene silencing by either preventing or promoting the recruitment of regulatory proteins to DNA (Prendergast*et al*., 1991; Watt*et al*., 1988) or can also mediate gene repression through interactions with histone deacetylases (HDACs) (Jones *et al*., 1998; Nan *et al*., 1998).

Recent studies have suggested that DNA methylation is also important for the regulation of non- CpG island promoters (Futscher*et al*., 2002; Hattori*et al*., 2004). In order to fully understand the global role of DNA methylation in normal tissue,it is essential to elucidate the role of non-CpG island methylation, as CpG islands has been found to occupy only approximately of 60% of human gene promoters(Wang *et al*., 2004).

Covalent Histone Modifications

Histone proteins consist of the nucleosome core, havinga globular C-terminal domain and N-terminal tail (Luger *et al*., 1997). The N-terminal tails of histones can undergo a variety of posttranslational covalent modifications like methylation, acetylation, ubiquitylation, sumoylation and phosphorylation on specific amino acid residues, resulting in the regulation of key cellular processes such as transcription, replication and repair (Kouzarides, 2007). These modifications are proposed to store the epigenetic memory inside a cell in the form of a 'histone code' that determines the structure and activity of different chromatin regions (Jenuwein*et al*., 2001). Histone modifications take place by either changing the chromatin accessibility or by recruitment of non-histone effector proteins. The mechanism of inheritance of the histone code, however, is still not fully understood.

Nucleosome Remodelling and Histone Variants

Non-covalent mechanism of nucleosome remodeling and presence of specialized histone variants, sometimes also plays an important role in regulation of chromatin structure and gene activity. Nucleosomes regulate gene expression by altering the accessibility of regulatory DNA sequences to transcription factorsin addition to its function as DNA packaging within a cell (Jiang *et al*., 2009). Nucleosome free regions (NFRs) present at the 5' and 3'ends of genes provide the sites for assembly and disassembly of the transcription machinery (Yuan *et al*., 2005). The nucleosome loss directly upstream of the transcription start site is strongly correlated with gene activation (Shivaswamy *et al*., 2008; Lin *et al*., 2007). Moreover, the presence of an NFR at gene promoters with basal level of transcription is related with the ability for rapid activation upon stimulation (Gal-Yam *et al*., 2006). In contrast, shutting off of the transcription start site within the NFR by a nucleosome is associated with gene repression (Schones *et al*., 2008). NFR modulation is achieved by ATP-dependent chromatin-remodeling complexes, which modifies the accessibility of DNA regulatory sitesthrough both sliding and ejection of nucleosomes (Smith *et al*., 2005). The interaction between nucleosome remodeling machinery, DNA methylation and histone modifications plays a vital role in establishing global gene expression patterns and chromatin design (Harikrishnan *et al*., 2005; Wysocka *et al*., 2006).

Non-coding RNA like miRNAs

miRNAs are small, approximately 22 nucleotides, non-coding RNAs that regulate gene expression through posttranscriptional silencing of target genes. Sequence-specific base pairing of miRNAs with 3'untranslated regions of target mRNA within the RNA-induced silencing complex results in degradation of target messenger RNA or inhibition of translation (He *et al*., 2004). miRNAs are expressed in a tissue-specific manner and control a wide array of biological processes including cell proliferation, apoptosis and differentiation. The list of miRNAs identified in the human genome and their potential target genes is growing rapidly, demonstrating their extensive role in maintaining global gene expression patterns (Zhang *et al*., 2007).

Like normal genes, the expression of miRNAs can be regulated by epigenetic mechanisms (Saito *et al*., 2006). In addition, miRNAs can also modulate epigenetic regulatory mechanisms inside a cell by targeting enzymes responsible for DNA methylation (DNMT3A and DNMT3B) and histone modifications (EZH2) (Fabbri*et al*., 2007; Friedman *et al*., 2009). Such interaction among the various components of the epigenetic machinery re-emphasizes the integrated nature of epigenetic mechanisms involved in the maintenance of global gene expression patterns.

Table 1: Effect of Environmental Chemicals on epigenetic changes of various diseases

Envi-ronmental Chemicals	Epigenetic Changes	Details of study	Diseases studied	References
Air Pollution	**DNA methylation** Global hypomethylation	Human PBL (*In vivo*)	Various cancers and Schizophrenia	Baccarelli et al.,2009; Smith *et al*.,2007;Roman-Gomez *et al*.,2006; Deng *et al*.,2006; Brothman *et al*.,2005; Shimabukuro *et al*.,2007
	iNOS hypomethylation	Human PBL (*In vivo*)	Lung cancer	Tarantini *et al*.,2009; Pereira *et al*.,2007
	Global hypermethylation	C57BL/CBA mice sperm (*In vivo*)	Colorectal cancer renal cell carcinoma, acute lymphoblastic leukaemia and bladder urothelial cell carcinoma	Yauk *et al*.,2008; Cheetham *et al*.,2008; Alemayehu *et al*.,2008; Norrie *et al*.,2002; Minardi *et al*.,2009;Schafer *et al*.,2010; Owen *et al*.,2010
	Hypermethylation of IFNg and hypomethylation of IL4	CD4+T-Lymphocytes (*In vivo*)	Asthma	Liu *et al*.,2008
	Histone modification Increased H3K4 dimethylation and H3K9 acetylation	Human PBL(*In vivo*)	Diabetic nephropathy	Cantone *et al*.,2011; Sayyed *et al*.,2010
	Global hypomethylation (Alu, LINE-1)	Human buffy coat (*In vivo*)	Various cancers and schizophrenia	Klein *et al*.,2002; Smith *et al*.,2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006;Brothman *et al*.,2005; Shimabukuro *et al*.,2007
	miRNAs Increased miR-222	Human PBL(*In vivo*)	Various cancers	Klein *et al*.,2002;Felli *et al*.,2005; le Sage *et al*.,2007; Garofalo *et al*.,2009
	Increased miR-21	Human PBL (*In vivo*)	Various cancers	Klein *et al*.,2002;Connolly *et al*.,2008; Chan *et al*.,2005; Iorio *et al*.,2005;Frankel *et al*.,2008; Zhu *et al*.,2007; Schetter *et al*.,2008; Bloomston *et al*.,2007; Meng *et al*.,2007
Alumini-um	**miRNAs** Increased miR-146a	HN cells (*In vitro*)	AD, cardiac hypertrophy and various cancers	Pogue *et al*.,2009; Lukiw *et al*.,2008;Pogue *et al*., 2009; Cheng *et al*.,2007; Volinia *et al*.,2006; Taganov *et al*.,2006; Bhaumik *et al*.,2008; Shen *et al*.,2008; Calin *et al*.,2005;Xu *et al*.,2008;Yanaihara *et al*.,2006; Kozaki *et al*.,2008

	Increased miR-9, miR-128, miR-125b	HN cells (*In vitro*)	AD, neurodegeneration and various cancers	Lukiw *et al*., 2007; Saba *et al*., 2008; Roehle *et al*., 2008; Wang *et al*., 2008; Tan *et al*., 2010; Veerla *et al*., 2009
Arsenic	**DNA methylation** Global hypomethylation	Human HaCaT keratinocytes, human prostate epithelial cell line RWPE-1, TRL 1215 rat liver epithelial cell line, V79-Cl3 Chinese hamster cells (*In vitro*)	Various cancers and schizophrenia	Reichard *et al*., 2007; Benbrahim-Tallaa *et al*., 2005; Coppin *et al*., 2008; Zhao *et al*.,1997; Sciandrello *et al*.,2004; Smith *et al*.,2007;Roman-Gomez *et al*.,2006; Deng *et al*.,2006; Brothman *et al*.,2005;Shimabukuro *et al*.,2007
		129/SvJ mice,84 fisher 344 Rat,86 homozygous Tg.AC mice,87 goldfish,232 human PBL233 (*In vivo*)	Various cancers and schizophrenia	Chen *et al*.,2004; Uthus *et al*.,2005; Xie *et al*.,2004; Smith *et al*.,2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006; Brothman *et al*.,2005;Shimabukuro *et al*.,2007
	Global hypomethylation and c-Ha-ras hypomethylation	C57BL/6J mice (*In vivo*)	Various cancers and schizophrenia	Okoji *et al*., 2002; Smith *et al*., 2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006; Brothman *et al*.,2005;Shimabukuro *et al*.,2007
	Global hypermethylation	Human PBL (*In vivo*)	Colorectal cancer, renal cell carcinoma, acute lymphoblastic leukaemia and bladder urothelial cell carcinoma	Majumdar *et al*.,2010; Pilsner *et al*.,2007; Cheetham *et al*.,2008; Alemayehu *et al*.,2008; Norrie *et al*.,2002; Minardi *et al*.,2009; Schafer *et al*.,2010; Owen *et al*.,2010;
	DAPK hypermethylation	Human uroepithelial SV-HUC-1 cells (*In vitro*)	Various cancers	Chai *et al*.,2007; Qian *et al*.,2010; Laytragoon-Lewin *et al*.,2010; Paluszczak *et al*.,2011; Hafner *et al*.,2011; Li *et al*.,2011; Ben Ayed-Guerfali *et al*.,2011; Sugita *et al*.,2011; Zhang *et al*.,2011; Hu *et al*.,2010; Van der Auwera *et al*.,2010; Zhang *et al*.,2011; Peng *et al*.,2010
	P16 hypermethylation	Human myeloma cell line U266 (*In vitro*)	Various cancers	Fu *et al*.,2005; Laytragoon-Lewin *et al*.,2010; Hu *et al*.,2010; Zhang *et al*.,2011; Malhotra *et al*.,2010; Poetsch *et al*.,2011; Lin *et al*.,2012; Wang *et al*.,2011; Zainuddin *et al*.,2011; Shaw *et al*.,2010
	DBC1, FAM83A, ZSCAN12 and C1QTNF6 hypermethylation	Human UROtsa cells (*In vitro*)	Bladder cancer, breast cancer and malignant lymphoproliferative	Jensen *et al*.,2008; Serizawa *et al*.,2011; Hill *et al*.,2010; Gronbaek *et al*., 2008

			neoplasms	
	P53 hypermethylation	Human lung adenocarcinoma A549 cells (*In vitro*)	Breast cancer and hepatoblastoma	Mass *et al*.,1997; Radpour *et al*.,2010; Hanafusa *et al*.,2005
	C-myc hypomethylation	TRL 1215 rat liver epithelial cells (*In vitro*)	Gastric cancer, colon cancer, liver cancer, kidney cancer and bladder cancer	Chen *et al*.,2001; Pereira *et al*.,2001; Luo *et al*.,2010; Fang *et al*.,1996; Tsujiuchi *et al*.,1999; Shen *et al*.,1997; Del *et al*.,1989
	C-myc and c-Ha-ras hypomethylation	Syrian hamster embryo cells (*In vitro*)	Gastric cancer, colon cancer, liver cancer, kidney cancer and bladder cancer	Takahashi *et al*.,2002;Pereira *et al*.,2001; Luo *et al*.,2010; Fang *et al*.,1996; Tsujiuchi *et al*.,1999; Shen *et al*.,1997; Del *et al*.,1989
	P16 and RASSF1 hypermethylation	A/J mice (*In vivo*)	Various cancers	Cui *et al*.,2006; Laytragoon-Lewin *et al*.,2010; Hu *et al*.,2010; Zhang *et al*.,2011; Malhotra *et al*.,2010; Poetsch *et al*.,2011; Lin *et al*.,2012; Wang *et al*.,2011; Zainuddin *et al*.,2011; Shaw *et al*.,2010; Rabiau *et al*.,2009; Buckingham *et al*.,2010
	Global hypomethylation and ER-alpha hypomethylation	C3H mice (*In vivo*)	Various cancersand schizophrenia	Waalkes *et al*.,2004; Smith *et al*.,2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006;Brothman *et al*.,2005; Shimabukuro *et al*.,2007
	P53 and P16 hypermethylation	Human PBL (*In vivo*)	Various cancers	Chanda *et al*.,2006;Laytragoon-Lewin *et al*.,2010; Hu *et al*.,2010; Zhang *et al*.,2011; Malhotra *et al*.,2010; Poetsch *et al*.,2011; Lin *et al*.,2012; Wang *et al*.,2011; Zainuddin *et al*.,2011; Shaw *et al*.,2010; Radpour *et al*.,2010; Hanafusa *et al*.,2005
	DAPK hypermethylation	Human bladder, kidney and ureter (*In vivo*)	Various cancers	Chen *et al*.,2007;Qian *et al*.,2010; Laytragoon-Lewin *et al*.,2010; Paluszczak *et al*.,2011; Hafner *et al*.,2011; Li *et al*.,2011; Ben Ayed-Guerfali *et al*.,2011; Sugita *et al*.,2011; Zhang *et al*.,2011; Hu *et al*.,2010; Van der Auwera *et al*.,2010; Zhang *et al*.,2011; Peng *et al*.,2010
	RASSF1A and PRSS3 hypermethylation	Human bladder (*In vivo*)	Lung cancer and prostate cancer	Marsit *et al*.,2006;Rabiau *et al*.,2009; Buckingham *et al*.,2010
	P16 hypermethylation	Human PBL (*In vivo*)	Various cancers	Zhang *et al*.,2007; Laytragoon-Lewin *et al*.,2010; Hu *et al*.,2010; Zhang *et al*.,2011;

				Malhotra *et al*.,2010; Poetsch *et al*.,2011; Lin *et al*.,2012; Wang *et al*.,2011; Zainuddin *et al*.,2011; Shaw *et al*.,2010
	P53 hypermethylation	Human basal cell carcinoma (*In vivo*)	Breast cancer and hepatoblastoma	Boonchai *et al*.,2000; Radpour *et al*.,2010; Hanafusa *et al*.,2005
	Both hypomethylation and hypermethylation of VHL	Human kidney cells (*In vitro*)	Renal cell carcinoma	Zhong *et al*.,2001
	Histone modification			
	Decreased H3 acetylation	UROtsa and URO-ASSC cells (*In vitro*)	Renal cell carcinomas	Jensen *et al*.,2008; Kanao *et al*.,2008
	Decreased H4K16 acetylation	UROtsa cells (*In vitro*)	Bladder cancer	Jo *et al*.,2009
	Increased H3K14 acetylation Increased H3S10 phosphorylation	NB4 cells (*In vitro*)	Diabetic nephropathy	Li *et al*.,2002; Sayyed *et al*.,2010
	Increased H3 phosphorylation	WI-38 human diploid fibroblast cells(*In vitro*)	Diabetic nephropathy	Li *et al*.,2003; Sayyed *et al*.,2010
	Increased H3K9 acetylation	HepG2 hepatocarcinoma cells(*In vitro*)	Diabetic nephropathy	Ramirez *et al*.,2008; Sayyed *et al*.,2010
	Decreased H3, H4, H2a, H2b acetylation Decreased H3 and H4 methylation Increased H2b methylation	Drosophila melanogaster tissue culture cell line KC161(*In vitro*)	Heart disease and traumatic brain injury	Arrigo *et al*.,1983; Gaikwad *et al*.,2010; Gao *et al*.,2006
	Increased H3K36 trimethylation Decreased H3K36 dimethylation Increased H3K4 dimethylation	Human lung carcinoma A549 cells (*In vitro*)	Diabetic nephropathy, multiple myeloma and prostate cancer	Zhou *et al*.,2008; Sayyed *et al*.,2010; Zhao *et al*.,2010; Seligson *et al*.,2009
	Increased H3K9 dimethylation Decreased H3K27 trimethylation Increased H3K4 trimethylation	Human lung carcinoma A549 cells (*In vitro*)	Prostate cancer, kidney cancer, lung cancer, HCC and AML	Zhou *et al*.,2008; Seligson *et al*.,2009; Arita *et al*.,2009; Chen *et al*.,2010; Yao *et al*.,2010; Paul *et al*.,2010
	Increased H2AX phosphorylation	RPMI7951 melanoma cells (*In vitro*)	Ataxia telangiectasia	Zykova *et al*.,2006; Porcedda *et al*.,2008
	Decreased H3K18 acetylation Decreased H3R17 methylation	1470.2 cell line derived from the mouse a denocarcinoma parent line (*In vitro*)	Prostate cancerand colon cancer	Barr *et al*.,2009; Seligson *et al*.,2009; Ashktorab *et al*.,2009
	miRNAs			
	Increased miR-222, Decreased miR-210	TK6 cell line (*In vitro*)	Various cancersand AD	Marsit *et al*.,2006; Felli *et al*.,2005; le Sage *et al*.,2007; Garofalo *et al*.,2009; Mi *et al*.,2007; Saumet *et al*.,2009; Hebert *et al*., 2008

	Decreased miR-19a	T24 cell line (*In vitro*)	Various cancers	Cao *et al*.,2011; Takakura *et al*.,2008; Calin *et al*.,2004; Arndt *et al*.,2009; Bandres *et al*.,2006; Malzkorn *et al*.,2010; Hebert *et al*.,2007; Budhu *et al*.,2008; Connolly *et al*.,2008; Hayashita *et al*.,2005
Benzene	**DNA methylation** Global hypomethylation (Alu, LINE-1)	Human PBL (*In vivo*)	Various cancers and schizophrenia	Baccarelli *et al*.,2009; Smith *et al*.,2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006;Brothman *et al*.,2005; Shimabukuro *et al*.,2007
	P15 hypermethylation and melanoma antigen-1 (MAGE-1) hypomethylation	Human PBL (*In vivo*)	Psoriasis and various cancers	Kim *et al*.,2007; Bassil *et al*.,2007; Koutros *et al*.,2010; Waggoner *et al*.,2011; Bollati *et al*.,2007; Zhang *et al*.,2009; Furonaka *et al*.,2004; Lindberg *et al*.,2008; Kim *et al*.,2009; Shimamoto *et al*.,2005; Chen *et al*.,2002; Gallardo *et al*.,2004; El-Shakankiry *et al*.,2006; Matsuno *et al*.,2005; Wemmert *et al*.,2009; Berg *et al*.,2007; Wong *et al*.,2003
	Global DNA hypomethylation	Human lymphoblastoid cell line TK6 (*In vitro*)	Various cancers and schizophrenia	Ji *et al*.,2010; Smith *et al*.,2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006;Brothman *et al*.,2005; Shimabukuro *et al*.,2007
	Hypermethylation of poly (ADP-ribose) polymerases-1 (PARP-1)	Lymphoblastoid cell line F32 (*In vitro*)	Various cancers	Gao *et al*.,2010
Bisphenol A	**DNA methylation** Hypomethylation of the Agouti gene and CabpIAP	Mouse embryo (*In vivo*)	Mice with hypomethylation of the Agouti gene are obese, diabetic and exhibit increased cancer rates	Dolinoy *et al*.,2007; Morgan *et al*.,2010; Xiang *et al*.,2010
	Hypomethylation of the homeobox gene Hoxa10	CD-1 mice (*In vivo*)	Not applicable	Bromer *et al*.,2010;
	Hypermethylation of LAMP3.	Breast epithelial cells (*In vitro*)	Breast cancer	Weng *et al*.,2010;
	miRNAs Increased miR-146a	3A placental cells (*In vitro*)	Cardiac hypertrophy, AD and various cancers	Whiting *et al*.,2010; Lukiw *et al*.,2008; Pogue *et al*.,2009; Cheng *et al*.,2007; Volinia *et al*.,2006; Taganov *et al*.,2006; Bhaumik *et al*.,2008; Shen *et al*.,2008; Calin *et al*.,2005; Xu *et al*.,2008; Yanaihara *et al*.,2006; Kozaki *et al*.,2008;

Cadmium	**DNA methylation** Global DNA hypomethylation	K562 cell *(In vitro*)	Colorectal cancer, renal cell carcinoma, acute lymphoblastic leukaemia,bladder urothelial cell carcinoma	Huang *et al*.,2008; Cheetham *et al*.,2008; Alemayehu *et al*.,2008; Norrie *et al*.,2002; Minardi *et al*.,2009; Schafer *et al*.,2010; Owen *et al*.,2010
	Initially induces DNA hypomethylation, prolonged exposure results in DNA hypermethylation	TRL1215 rat liver cells (*In vitro*)	Not applicable	Takiguchi *et al*.,2003;
	miRNAs Decreased miR-146a	Human PBL (*In vivo*)	Various cancers	Bollati *et al*.,2010; Gramantieri *et al*.,2007; Jazdzewski *et al*.,2008; Lin *et al*.,2008
Chromium	**DNA methylation** P16 and hMLH1 hypermethylation	Human lung (*In vivo*)	Various cancers	Kondo *et al*.,2006; Takahashi *et al*.,2005; Laytragoon-Lewin *et al*.,2010; Hu *et al*.,2010; Zhang *et al*.,2011; Malhotra *et al*.,2010; Poetsch *et al*.,2011; Lin *et al*.,2012; Wang *et al*.,2011; Zainuddin *et al*.,2011; Shaw *et al*.,2010; Gonzalez-Ramirez *et al*.,2011; Vasavi *et al*.,2010; Ling *et al*.,2010
	Gpt hypermethylation	G12 cell line (*In vitro*)	Not applicable	Klein *et al*.,2002
	Histone modification Decreased H3S-10 Phosphorylation Decreased H3K4 trimethylation Decreased H3 and H4 acetylation Increased Dimethylation and trimethylation of H3K9 and H3K4 Decreased H3K27trimethylation and H3R2 dimethylation	Human lung carcinoma A549 cells (*In vitro*)	Type 2 diabetes, heart disease and traumatic brain injury	Arita *et al*.,2009; Sayyed *et al*.,2010; Gaikwad *et al*.,2010; Gao *et al*.,2006
DES	**miRNAs** Decreased miR-9-3	Breast epithelial cells (*In vitro*)	Breast cancer	Hsu *et al*.,2009
Dioxin	**DNA methylation** Igf2 hypomethylation	Rat liver (*In vivo*)	Russell–Silver syndrome and various cancers	Wang *et al*.,2007; Gucev *et al*.,2009; Zeschnigk *et al*.,2008; Chopra *et al*.,2010; Dammann *et al*.,2010; Baba *et al*.,2010; Li *et al*.,2009; Cui *et al*.,2002; Ito *et al*.,2008
	Alterations in DNA methylation at multiple genomic regions	Splenocyte of mice (*In vivo*)	Not applicable	McClure *et al*.,2011
Drinking Water	**DNA methylation** Global hypomethylation c-myc hypomethylation	Mice liver (*In vivo*)	Gastric cancer, colon cancer, liver cancer, kidney cancer and bladder cancer	Pereira *et al*.,2001; Coffin *et al*.,2000; Luo *et al*.,2010; Fang *et al*.,1996; Tsujiuchi *et al*.,1999; Shen *et al*.,1997; Del *et al*.,1989

Lead	**DNA methylation** Global hypomethylation	Human PBL, newborn umbilical cord blood samples(*In vivo*)	Various cancersand schizophrenia	Wright *et al*.,2010; Pilsner *et al*.,2009; Smith *et al*.,2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006;Brothman *et al*.,2005; Shimabukuro *et al*.,2007
Mercury	**DNA methylation** Global hypomethylation Rnd2 hypermethylation	Brain tissues in polar bear(*In vivo*) Mouse embryonic stem cells(*In vitro*)	Neurological disorders and various cancer Neuronal migration defect	Pilsner *et al*.,2010; Mill *et al*.,2008; Wang *et al*.,2008; Esteller *et al*.,2008 Arai *et al*.,2011; Heng *et al*.,2008
Nickel	**DNA methylation** ATF-1, HIF-1, gpt and Rb hypermethylation P16 hypermethylation **Histone modification** Increased H3K9 methylation Decreased Acetylation at all four core histones Increased H3K9 dimethylation Increased H2a, H2b ubiquitylation Decreased H3K4 methylation Decreased H3K4 acetylation Decreased H2a, H2b, H3, H4 acetylation DecreasedH4K5, H4K8, H4K12, H4K16 acetylation DecreasedH2A, H2B, H3, H4 acetylation (especially in H2BK12 and H2BK20) Increased H3 phosphorylation	G12 cell line (*In vitro*) Mouse histiocytomas (*In vivo*) Human lung carcinoma A549 cells (*In vitro*) Human lung carcinoma A549 cells,G12 cells, 1HAEo- cell line, human (HAE) and rat (NRK) cells, Chinese hamster cell line (*In vitro*) Human lung carcinoma A549 cells (*In vivo*) Human airway epithelial 1HAEo(HAE) cell line (*In vitro*) Human lung carcinoma A549 cells (*In vitro*)	Various cancers Various cancers Heart disease and traumatic brain injury Lung cancer, heart disease, chronic glomerular disease and traumatic brain injury Ataxia telangiectasia Heart disease and traumatic brain injury Diabetic nephropathy	Lee *et al*.,1995; Chim *et al*.,2003; Stirzaker *et al*.,1997; Chen *et al*.,2004; Zhao *et al*.,2010; Zhao *et al*.,2003; Li *et al*.,1998 Govindarajan *et al*.,2002; Laytragoon-Lewin *et al*.,2010; Hu *et al*.,2010; Zhang *et al*.,2011; Malhotra *et al*.,2010; Poetsch *et al*.,2011; Lin *et al*.,2012; Wang *et al*.,2011; Zainuddin *et al*.,2011; Shaw *et al*.,2010 Chen *et al*.,2006; Ke *et al*.,2006; Gaikwad *et al*.,2010; Gao *et al*.,2006 Lee *et al*.,1995; Karaczyn *et al*.,2005; Karaczyn *et al*.,2006; Broday *et al*.,2000; Chen *et al*.,2006; Ke *et al*.,2006; Klein *et al*.,1997; Yan *et al*.,2003; Arita *et al*.,2009; Gaikwad *et al*.,2010; Gao *et al*.,2006; Chen *et al*.,2010; Lefevre *et al*.,2010 Broday *et al*.,2000; Kumar *et al*.,2011 Golebiowski *et al*.,2005; Gaikwad *et al*.,2010; Gao *et al*.,2006; Ke *et al*., 2008; Sayyed *et al*., 2010
Pesticides	**DNA methylation** P53 hypermethylation Alter DNA methylation in the germ line Hypomethylation of c-jun	Human lung adenocarcinoma A549 cells (*In vitro*) Rat testis (*In vivo*) Mouse liver (*In vivo*)	Breast cancer and hepatoblastoma Potential effects in the offspring Gastric cancer, colon	Mass *et al*.,1997; Radpour *et al*.,2010; Hanafusa *et al*.,2005 Anway *et al*.,2005; Guerrero-Bosagn *et al*.,2010; Anway *et al*.,2006 Tao *et al*.,2000; Pereira *et*

	and c-myc		cancer, liver cancer, kidney cancer and bladder cancer	*al*.,2001; Luo *et al*.,2010; Fang *et al*.,1996; Tsujiuchi *et al*.,1999; Shen *et al*.,1997 Del *et al*.,1989
	Global hypomethylation (Alu)	Human PBL(*In vivo*)	Various cancersand schizophrenia	Rusiecki *et al*.,2008; Kim *et al*.,2010; Smith *et al*.,2007; Roman-Gomez *et al*.,2006; Deng *et al*.,2006;Brothman *et al*.,2005; Shimabukuro *et al*.,2007
	Both hypomethylation and hypermethylation of VHL	Human kidney cells (*In vitro*)	Renal cell carcinoma	Zhong *et al*.,2001
	Histone modification- Increased Ac of H3 and H4	Immortalized rat mesencephalic/ dopaminergic cells (N27 cells) (*In vitro* and *in vivo*)	Parkinson's disease	Song *et al*.,2010
RDX	**miRNAs** Increased let-7, miR-15, miR-16, miR-26, miR-181 Decreased miR-10b	Mouse brain and liver (*In vivo*)	Various cancers	Zhang *et al*.,2009; Calin *et al*.,2005; Calin *et al*.,2002; Cimmino *et al*.,2005; Ambs *et al*.,2008; Roccaro *et al*.,2009; Johnson *et al*.,2005; Lee *et al*.,2007; Yanaihara *et al*.,2006; Sampson *et al*.,2007
	Increased miR-206, miR-30, miR-195	Mouse brain and liver (*In vivo*)	Various cancers	Zhang *et al*.,2009; Iorio *et al*.,2005; Adams *et al*.,2007; Roccaro *et al*.,2009; Dixon-McIver *et al*.,2008; van Rooij *et al*.,2006; Sayed *et al*.,2007

PBL: Peripheral blood leucocytes; HCC: Hepatocellular carcinoma; AML: Acute myeloid leukaemia; AD: Alzheimer's disease; HN cells: Human neural cells; RDX: Hexahydro-1,3,5-trinitro-1,3,5-triazine; DES: Diethylstilbestrol.

Suitable study designs, approaches, challenges and opportunities for Environmental Epigenomics Studies

The rapid growth of environmental epigenetics field in the past several years has led the investigators to face different difficulties and challenges as well. Few studies had produced uneven results on same environmental chemicals that may be because of several factors. The fact that these tissue specific epigenetic alterations (Minard *et al*., 2009) is likely to be acceptable because same environmental chemical might produce different epigenetic changes in different tissues, and even it can change within the same tissue on different cell types. Difference in study design, laboratory methods and small sample size may also be major causes for these inconsistencies in epigenetic changes. Replication of results and identification of the sources of variability across studies is one of the major challenges for epigenetic investigations. There relationship between a disease and an epigenetic marker can be determined by an effect of disease on the epigenetic patterns, instead of vice versa (Reltone*t al*., 2010), since epigenetic markers change over time. The epigenetic alterations that were found to be induced by or associated with environmental pollutants were also found in various diseases. Earlier prospective epidemiological studies might be helpful for mapping epigenomic changes in response to specific chemicals. Methods of collection and processing can modify the cell types stored, thus potentially having its effect on epigenetic marks. In addition to this, high through put methods providing good quality data on DNA methylation, histone modifications and miRNA expression are gradually used these days in human investigations. The share of the effects of any particular environmental exposure that can mediate through epigenetic mechanisms is still undetermined, though epigenetic mechanisms are ideal molecular intermediates of environmental effects. Statistical approaches, including well-designed prospective studies and advanced statistical methods are urgently needed for causal inference in this regard. The epidemiological causal reasoning in epigenomics should include careful consideration of knowledge, data, methods and techniques from several disciplines similar to genomic

studies (Geneletti *et al*., 2011).

Epigenomics: Can it be used for prevention of various diseases

One of the main objectives behind these epidemiology investigations is to look for future preventive interventions. Various clinical and preclinical studies has already showed that most of the epigenetic changes are reversible, which offers novel insights to develop new preventive and therapeutic strategies in this field that can make use of molecules that alter the activities of epigenetic enzymes, such as DNA Methyl Transferases (DNMTs) and Histone Deacetylases (HDACs). Drugs have already been designed and developed in this regard that produce functional effects like histone acetylation and DNA hypomethylation that can be used to restore the normal gene transcription. Future epidemiology studies and epigenomic research to evaluate the effects of environmental exposures on the epigenome may provide information for developing preventive strategies, including exposure reduction, along with pharmacological, dietary or lifestyle interventions as well.

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