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 on opportunities, 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

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 in approximately 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). 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 occurring without a change in the nucleotide sequence (Bird, 2007). These changes in phenotypic traits occur due to variety of mechanisms (Fradin and Bougnères, 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 remodelling 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 most thoroughly 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 most of 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; Wattet 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, having 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 remodelling 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 factors in 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 sites through both sliding and ejection of nucleosomes (Smith et al., 2005). The interaction between nucleosome remodelling 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

<table>
<thead>
<tr>
<th>Environmental Chemicals</th>
<th>Epigenetic Changes</th>
<th>Details of study</th>
<th>Diseases studied</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Pollution</td>
<td>DNA methylation</td>
<td>Human PBL (In vivo)</td>
<td>Various cancers and schizophrenia</td>
<td>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</td>
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<td>Global hypomethylation</td>
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<td>iNOS hypomethylation</td>
<td>Human PBL (In vivo)</td>
<td>Lung cancer</td>
<td>Tarantini et al., 2009; Pereira et al., 2007</td>
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<td></td>
<td>Global hypermethylation</td>
<td>C57BL/CBA mice sperm (In vivo)</td>
<td>Colorectal cancer renal cell carcinoma, acute lymphoblastic leukaemia and bladder urothelial cell carcinoma</td>
<td>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</td>
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<td></td>
<td>Hypermethylation of IFNg and hypomethylation of IL4</td>
<td>CD4+T-Lymphocytes (In vivo)</td>
<td>Asthma</td>
<td>Liu et al., 2008</td>
</tr>
<tr>
<td>Histone modification</td>
<td>Increased H3K4 dimethylation and H3K9 acetylation</td>
<td>Human PBL (In vivo)</td>
<td>Diabetic nephropathy</td>
<td>Cantone et al., 2011; Sayyed et al., 2010</td>
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<td>Global hypomethylation (Alu, LINE-1)</td>
<td>Human buffy coat (In vivo)</td>
<td>Various cancers and schizophrenia</td>
<td>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</td>
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<td>miRNAs</td>
<td>HN cells (In vitro)</td>
<td>AD, cardiac hypertrophy and various cancers</td>
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<td>Arsenic DNA methylation</td>
<td>Human HaCaT keratinocytes, human prostate epithelial cell line RWPE-1, TRL 1215 rat liver epithelial cell line, V79-CI3 Chinese hamster cells (<em>In vitro</em>)</td>
<td>Various cancers and schizophrenia</td>
<td>Reíchard et al., 2007; Benbrahim-Tallaa et al., 2005; Coppin et al., 2008; Zhao et al.,1997; Scianrello et al.,2004; Smith et al.,2007; Roman-Gomez et al.,2006; Deng et al.,2006; Brothman et al.,2005; Shimabukuro et al.,2007</td>
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<td>Arsenic DNA methylation</td>
<td>129/SvJ mice, 84 fisher 344 Rat, 86 homozygous Tg.AC mice, 87 goldfish, 232 human PBL 233 (<em>In vivo</em>)</td>
<td>Various cancers and schizophrenia</td>
<td>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</td>
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<td>Human myeloma cell line U266 (<em>In vitro</em>)</td>
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<td>Bladder cancer, breast cancer and malignant lymphoproliferative</td>
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<td>Methylation Event</td>
<td>Tumor Type</td>
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<td>C-myc hypomethylation</td>
<td>TRL 1215 rat liver epithelial cells (In vitro)</td>
<td>Gastric cancer, colon cancer, liver cancer, kidney cancer and bladder cancer</td>
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<td>Gastric cancer, colon cancer, liver cancer, kidney cancer and bladder cancer</td>
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<td>Lung cancer and prostate cancer</td>
<td>Marsit et al., 2006; Rabiau et al., 2009; Buckingham et al., 2010</td>
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| 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;
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<th>P53 hypermethylation</th>
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<td>Various cancers and AD</td>
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| Human basal cell carcinoma (In vivo) | Breast cancer and hepatoblastoma |
| Human kidney cells (In vitro) | Renal cell carcinoma |
| UROtsa and URO-ASSC cells (In vitro) | Renal cell carcinomas |
| UROtsa cells (In vitro) | Bladder cancer |
| NB4 cells (In vitro) | Diabetic nephropathy |
| WI-38 human diploid fibroblast cells (In vitro) | Diabetic nephropathy |
| HepG2 hepatocarcinoma cells (In vitro) | Diabetic nephropathy |
| Drosophila melanogaster tissue culture cell line KC161 (In vitro) | Heart disease and traumatic brain injury |
| Human lung carcinoma A549 cells (In vitro) | Diabetic nephropathy, multiple myeloma and prostate cancer |
| Human lung carcinoma A549 cells (In vitro) | Prostate cancer, kidney cancer, lung cancer, HCC and AML |
| RPMI7951 melanoma cells (In vitro) | Ataxia telangiectasia |
| 1470.2 cell line derived from the mouse a denocarcinoma parent line (In vitro) | Prostate cancer and colon cancer |

- Malhotra et al., 2010; Poetsch et al., 2011; Lin et al., 2012; Wang et al., 2011; Zaimuddin et al., 2011; Shaw et al., 2010
- Boonchai et al., 2000; Radpour et al., 2010; Hanafusa et al., 2005
- Zhong et al., 2001
- Jensen et al., 2008; Kanao et al., 2008
- Jo et al., 2009
- Li et al., 2002; Sayyed et al., 2010
- Li et al., 2003; Sayyed et al., 2010
- Ramirez et al., 2008; Sayyed et al., 2010
- Arrigo et al., 1983; Gaikwad et al., 2010; Gao et al., 2006
- Zhou et al., 2008; Sayyed et al., 2010; Zhao et al., 2010; Seligson et al., 2009
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- Zykova et al., 2006; Porcedda et al., 2008
- Barr et al., 2009; Seligson et al., 2009; Ashktorab et al., 2009
- 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
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<td>Psoriasis and various cancers</td>
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<td>Various cancers and schizophrenia</td>
</tr>
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<td>Global DNA hypomethylation</td>
<td>Human lymphoblastoid cell line TK6 (In vitro)</td>
<td>Various cancers and schizophrenia</td>
</tr>
<tr>
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<td>Hypermethylation of poly (ADP-ribose) polymerases-1 (PARP-1)</td>
<td>Lymphoblastoid cell line F32 (In vitro)</td>
<td>Various cancers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bisphenol A</th>
<th>DNA methylation</th>
<th>Mouse embryo (In vivo)</th>
<th>Mice with hypomethylation of the Agouti gene are obese, diabetic and exhibit increased cancer rates</th>
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<tbody>
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<td>Breast cancer</td>
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<td>Hypermethylation of LAMP3.</td>
<td>3A placental cells (In vitro)</td>
<td>Cardiac hypertrophy, AD and various cancers</td>
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<td>miRNAs</td>
<td>Increased miR-146a</td>
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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; 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; 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; Dolinoy et al.,2007; Morgan et al.,2010; Xiang et al.,2010; Bromer et al.,2010; Weng et al.,2010; 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;
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<th>miRNAs</th>
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<th>TRL1215 rat liver cells (In vitro)</th>
<th>Human PBL (In vivo)</th>
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<th>Various cancers</th>
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<th>Gpt hypermethylation</th>
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<td>Decreased miR-9-3</td>
<td>Igf2 hypomethylation</td>
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<td>Alterations in DNA methylation at multiple genomic regions</td>
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<td>Igf2 hypomethylation</td>
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<td>DNA methylation</td>
<td>Global hypomethylation</td>
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<td>Various cancers and schizophrenia</td>
<td>Wright <em>et al.</em>, 2010; Pilsner <em>et al.</em>, 2009; Smith <em>et al.</em>, 2007; Roman-Gomez <em>et al.</em>, 2006; Deng <em>et al.</em>, 2006; Brothman <em>et al.</em>, 2005; Shimabukuro <em>et al.</em>, 2007</td>
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<td>Rnd2 hypermethylation</td>
<td>Mouse embryonic stem cells (<em>In vitro</em>)</td>
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<td>Neuronal migration defect</td>
<td>Arai <em>et al.</em>, 2011; Heng <em>et al.</em>, 2008</td>
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<td>Decreased Acetylation at all four core histones</td>
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<td>Increased H2a, H2b ubiquitylation</td>
<td>Decreased H3K4 methylation</td>
<td>Decreased H3K4 acetylation</td>
<td>Decreased H2a, H2b, H3, H4 acetylation</td>
<td>Decreased H4K5, H4K8, H4K12, H4K16 acetylation</td>
<td>Decreased H2A, H2B, H3, H4 acetylation (especially in H2BK12 and H2BK20)</td>
<td>Increased H3 phosphorylation</td>
<td>Human lung carcinoma A549 cells (<em>In vivo</em>)</td>
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<td>P53 hypermethylation</td>
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<td>Breast cancer and hepatoblastoma</td>
<td>Mass <em>et al.</em>, 1997; Radpour <em>et al.</em>, 2010; Hanafusa <em>et al.</em>, 2005</td>
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<td>Alter DNA methylation in the germ line</td>
<td>Rat testis (<em>In vivo</em>)</td>
<td>Potential effects in the offspring</td>
<td>Anway <em>et al.</em>, 2005; Guerrero-Bosagn <em>et al.</em>, 2010; Anway <em>et al.</em>, 2006</td>
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<td>Hypomethylation of c-jun</td>
<td>Mouse liver (<em>In vivo</em>)</td>
<td>Gastric cancer, colon</td>
<td>Tao <em>et al.</em>, 2000; Pereira <em>et al.</em>, 2010</td>
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and c-myc

- Global hypomethylation (Alu)

- Histone modification:
  - Increased Ac of H3 and H4

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<tr>
<th>RDX</th>
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<td>Increased miR-206, miR-30, miR-195</td>
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**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 (Relton et 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 throughput 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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