Review Article **ISSN: 2349 – 4492**

Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: www.ajrbps.com

https://doi.org/10.36673/AJRBPS.2020.v08.i03.A12

ROLE OF EPIGENETICS IN ETIOLOGY AND PREVENTION OF HUMAN DISEASES: A REVIEW BASED ON CURRENT EVIDENCES

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ABSTRACT

In recent years, there has been an explosion of research on genetic causes of human diseases. Although genetic changes involve alteration of the genetic code, epigenetic changes are associated with external modifications to chromatin structure and gene expression without the alteration of the core DNA sequence. It is becoming increasingly evident that there are several disease-causing alterations in the epigenome. Thus, it is important to understand the etiology of human diseases with respect to epigenetic modifications. This review article focuses on the current advances in knowledge on human diseases that occur due to epigenetic dysregulation. We also highlight the role of epigenetics in diabetes regulation and in emerging viral infections. Understanding the significance of epigenetic changes and their role in disease development could help develop therapies targeting the epigenomic network of the cell.

KEYWORDS

DNA methylation, Histone modification and Epigenetic dysregulation.

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INTRODUCTON

The term epigenetics was first introduced by Conrad Waddington in the early 1940s[1]. Epigenetics involves the study of heritable changes in gene function that do not involve changes in the genetic code. Knowledge of epigenetics helps in understanding basic mechanisms where alterations of genes and gene products influence cell development. Epigenetic mechanisms directly influence gene expression at the transcriptional and translational levels and thus have the potential to

control overall gene expression. Epigenetic changes are known to regulate differentiation of pluripotent stem cells and determine the ultimate fate of the stem cell[2]. Epigenetic regulation is involved in a large spectrum of processes, including morphogenesis, differentiation, imprinting, gene silencing, position effect, reprogramming and carcinogenesis. Several different epigenetic mechanisms exist in the cell, which include including methylation of DNA, post-translational modifications (acetylation, phosphorylation and sumoylation) of his tone proteins and small RNA-mediated control of gene expression. Epigenetic modifications, and their subsequent effect on gene expression, are highly cell- and tissue-specific, enabling control of the gene expression profile in cells and tissues. These modifications are stable and are somatically heritable in dividing cells[3]. Thus, any aberration in the epigenetic state can result in altered tissue development and subsequent pathology. Recently, a wide range of human pathologies such as cancer, autoimmune disorders, diabetes, neurological disorders and interestingly, viral infections have been associated with de novo or inherited epigenetic changes[4,5]. In this review, we examine the development of the study of epigenetics, and its role in healthy physiology and disease pathologies. Understanding the etiology, which is the detailed study of underlying mechanisms of disease development of these epigenetic changes, will help in better disease management and in developing effective therapy.

TYPES OF EPIGENETIC MODIFICATIONS

Following the discovery of the chromosome in 1879 by Ian Fleming[6,7], further studies, such as those by Thomas Morgan, helped to understand the genetic linkage between various chromosomes and X chromosome to understand sex determination in Drosophila. In the 1930s, HJ Muller carried out pioneering work to understand chromosomal rearrangements and their effect on Drosophila phenotype. This work was followed by research by Reik and Surani, who provided compelling evidence of genomic imprinting and the consequences on embryonic development[8]. Studies by Allfrey *et al.* in the 1960s established that histones are post-translationally modified[9]. Extensive research following this pioneering discovery has shown that these modifications also alter gene expression patterns[10]. The most important of these modifications include histone 3 (H3) lysine 9 (K9) demethylation and lysine 27 (K27) trimethylation, which are involved in transition of heterochromatin to euchromatin and functional transcription of genes. With the advent of novel gene detection and sequencing technologies a wide array of epigenetic modifications have now been studied (Figure No.1), of which DNA methylation has been one of the most pioneering discoveries made in recent times. Many studies have since analyzed DNA methylation patterns and alteration of gene expression in various tissues. DNA methyltransferases are crucial in modifying methylation status of genes and play important roles in switching genes "on" and "off", leading to changes in gene expression. Studies on epigenetic regulation have been able to progress even further based on various microarray-based methods that have been developed. More recently, microRNAs (miRNA) and other non-protein coding RNAs (ncRNA) have been shown to regulate chromatin modification and thus gene expression[11]. miRNAs regulate approximately 60% of genes in humans and slowly, but steadily, the expression of many miRNAs is being shown to be epigenetically regulated by histone modification or DNA methylation at specific loci[12].

1. DNA methylation: CH_3 (methyl group) is added by DNA methyl transferases (DNMT) to tag DNA and is associated with gene activation and repression.
2. Histone modifications: The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA that may be activated or repressed.

Acetylation

$COCH_3$ (acetyl) group is added by histone acetyl transferases and is associated with gene activation.

Deacetylation

Acetyl group is removed by histone deacetyl (HDAC) transferases and is associated with gene repression.

EPIGENESIS AND EPIGENETIC REGULATION IN NORMAL PHYSIOLOGY

Epigenesis plays an important role during development[13,14]. Pluripotent stem cells in the embryo undergo differentiation to form tissue-specific oligo potent progenitor cells. Differentiation of pluripotent stem cells to their respective cell lineages is dependent upon the epigenetic changes in the genome that control the expression of specific genes. These epigenetic modifications alter the response of various transcriptional factors to hormones and other environmental cues. Thus, epigenesis plays an important role in overall determination of cellular fate and development of the whole organism.

The nature of epigenetic alterations has been understood by studying pluripotent stem cells[15]. Transition of adult somatic cells to pluripotent stem cells illustrates the major epigenetic changes that are involved in the whole process. Somatic cell programming during the transition involves a host of transcription factors, which include c-MYC, OCT-4, KLF4 and SOX2. The epigenetic landscape in pluripotent stem cells is maintained by genes such as *OCT4* and *NANOG*. Expression of these two genes are silenced in somatic cells by DNA methylation at their promoters and repressive histone modifications such as H3K27 trimethylation (H3K27me3). The DNA methyl transferase DNMT3 also serves as a marker of reprogramming cells. Reprogramming of adult cells and establishment of pluripotent cells is marked by the establishment of epigenetic changes associated with the genome. The variety of the changes that are seen include altered levels of H3K4 and H3K27 trimethylation at signature gene promoters, activation of inactive X chromosome in female pluripotent cells, DNA hypomethylation of the heterochromatin repeats and maintenance of DNA methylation patterns at imprinted genes. The onset of these various events results in the final step of chromatin fiber reorganization and thus affects the overall elasticity and flexibility of chromatin. These various changes are important for appropriate functioning of pluripotent stem cells. Aberrations in any of these events results in induction of apoptotic pathways and cell death[16].

ENVIRONMENTAL FACTORS GOVERNING EPIGENESIS

Epigenetic modifications are reversible. The genome is highly flexible and responds to a variety of environmental stimuli, such as nutrition and stress, as well as exposure to toxins and drugs. Food plays an important role in governing the overall growth and health of cells. Severe shortage of nutrition results in a lack of growth that could be the result of alteration of critical genes required for this. There is evidence that famines and a lack of nutritional food results in long term effects on the growth of children[17]. Poor nutrition also causes faulty imprinting of epigenetic signature sequences that results in development of neurological disorders and stress related disorders[18,19].

Folate, a water-soluble B vitamin, is one of the major nutritional components, which has been shown to affect epigenetic modifications[20]. It is an important cofactor for many of the methyl transferases and thus plays an important role in DNA methylation. Consequently, folate deficiency has been shown to be responsible for hypomethylation of DNA and subsequent development of colorectal cancer[21] and can also contribute to neural tube and crest defects during development[22].

Exposure to toxic metals in the environment can also have an impact on the overall etiology of disease. Exposure to arsenic is known to be associated with altered DNA methylation levels, histone modification machinery, and miRNA expression, resulting in carcinogenesis and associated neurological defects[23]. Prolonged use of certain drugs can also influence global epigenetic modifications. For instance, continuous use of oral contraceptive pills in women results in global hypomethylation of DNA[24]. In addition, the use of procainamide and hydralazine modifies the nuclear architecture and development of anti-nuclear antibodies, resulting in drug-induced lupus[25].

Stress is another major contributing factor in development of disease. People with post-traumatic stress disorder have altered levels of DNA methylation and gene expression when compared with those who have not been stressed[26]. Stress during pregnancy and perinatal stress has also been associated with the child developing neurological

and psychiatric disorders[27]. In addition, persistent exposure to pathogenic microorganisms results in modification of the genome and alteration in gene expression patterns[28]. Many microbes are known to modify the epigenomic machinery, including the histone modifying enzymes, resulting in persistent infection of individuals. Indeed, inflammation has been proposed to be the common pathway of stress-related diseases, which could be attributed to epigenetic modifications[29,30].

Physical exercise has also been identified as an important factor that helps in controlling cancer development and progression[31,32]. Physical exercise has been shown to up-regulate the expression of tumor suppressor genes, while down-regulating expression of oncogenes. Pathologies with dysregulated epigenetic modifications, which result in uncontrolled expression of several of the genes, can be regulated by physical activity[33].

HUMAN DISEASES CAUSED BY EPIGENETIC DYSREGULATION

There is increasing evidence that pathological epigenetic modifications are found in cancer, neurodegenerative diseases, and ageing (Figure No.2).

DNA and histone proteins are associated together by electrostatic interactions. DNA wraps around the histone proteins whose tails protrude from the structure. The epigenome is a series of chemical modifications that occur in DNA or specific amino acids in histone proteins that DNA is wrapped around. These act as markers that determine whether genes are active or inactive at certain times. These epigenetic changes are responsible for human diseases.

CANCER

Cancer is one of the most well studied pathologies where aberrant epigenetic modifications are involved in disease activity. Gross changes in DNA methylation patterns are seen in cancer cells when compared to non-cancerous cells. During tumorigenesis, both genome-wide and regional epigenetic changes occur, which drive tumor progression[34,35]. Hypermethylation of various promoter regions or repressive histone signatures on promoters result in the inactivation of tumor suppressor genes[36]. Hypermethylation of promoters, particularly in CpG island regions, for genes that support cell survival, such as *APC, RASSF1A* and *TP53*, is commonly observed in cancer cells. In fact, most cancers have distinct epigenetic alteration patterns. Non-small cell lung cancer exhibits levels of elevated DNMT, global deacetylated H3 and trimethylated H3K9[37,38,39]. DNMT1 and histone deacetylase 1 (HDAC1) are up-regulated during progression of pancreatic cancers in a malignancy-dependent manner and consequently deregulate genes that control the hallmarks of cancer proliferation, survival, angiogenesis, invasion and metastasis[40,41]. In colorectal cancer, global hypomethylation contributes to activation of various oncogenes, whereas hypermethylation in CpG islands promote tumorigenesis by silencing tumor suppressor genes. Multiple versions of translocation methylcytosine dioxygenase (TET1), an important DNA methylation regulator, were shown to be down-regulated in the early phases of tumorigenesis[42]. Histone modifications including loss of H3K20 trimethylation and di- and trimethylation of H3K4, H3K9 and H3K27 have been well documented in the pathogenesis of colorectal cancer[43].

AUTOIMMUNE DISEASES

Autoimmune diseases are another major class of diseases where epigenetic changes make a significant contribution to pathology[44]. In inflammation, DNA methylation contributes to T cell activation and function[45]. Dysregulated T cell functions are important in driving autoimmunity[46]. Global hypomethylation of DNA is observed in T cells from patients with systemic lupus erythematosus or rheumatoid arthritis[47]. In these patients, regional hypermethylation of promoters associated with HDAC1 and HDAC2 is observed[48]. Furthermore, the balance between HDACs and HATs is disturbed, resulting in hyperacetylation of histones H3 and H4. In osteoarthritis, regional H3K9 hypomethylation is associated with the pathophysiology[49]. In patients with sclerosis, hypomethylation at H3K27 me3 has been observed in CD4+ T cells as well in the white matter of the central nervous system[50].

NEURODEGENERATIVE DISEASES

Neurodegenerative disorders have a distinct epigenomic imprint which is different from healthy individuals. In both Alzheimer's disease (AD) and schizophrenia, reduced DNA methylation occurs at promoter regions for genes expressed in the central nervous system. In addition to methylation at the 5th position of the pyrimidine ring of cytosine (5mC), hydroxy-modified 5mC (5hmc) is present at high levels in the healthy brain and central nervous system[51]. Reductions in levels of 5mC and 5hmC and also in levels of DNMT have been observed in AD[52,53]. However, contrasting data has suggested that an increase in these levels was observed in the frontal cortex of AD patients[54]. This indicates that epigenetic modifications of gene expression in the nervous system is highly temporal and further study is warranted to fully understand the epigenetic program that underlies a healthy conditions. Decreased methylation is observed in the Alu repeat sequences of the genome in AD patients and this serves as one of the indicative features for prognosis of the disease[55]. Dementia and AD are also associated with alteredrhythmic methylation cycles of circadian rhythm protein $BMAL_1$ promoter resulting in rapid $BMAL_1$ degradation[56, 57]. In frontotemporal dementia, hypermethylation of the progranulin (*GRN*) promoter and potential hypermethylation of chromosome 9 open reading frame 72 *(C9ORF72)* promoter has been observed as a genetic mechanism involved in the pathology of this disease[58].

Abnormal methylation and global DNA hypomethylation are associated with autism and related disorders. Hypermethylation at the promoter region of the *FMR1* gene was found to be responsible for Fragile X syndrome, which may cause autism spectrum disorder[59]. Schizophrenia is associated with large number of changes mediated by epigenetic interactions[60]. The hypermethylation of sex-determining region Y-box containing gene 10 (*SOX10*) promoter in the brain leads to down-regulation of SOX10 expression, H3K27me3 hypomethylation at the glutamic acid decarboxylase 67 (GAD1) promoter, DNA hypomethylation at the *WDR18* gene, and elevated expression of DNMT1 and all these changes have been associated with schizophrenia[61].

DIABETES

According to statistics from WHO 2020, diabetes mellitus (DM) affects approximately 415 million people worldwide, of which 46% are undiagnosed and by 2040, 642 million will be affected. The most common types of DM present in the population are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is an autoimmune condition where pancreatic β-cells are destroyed, whereas T2DM is a metabolic condition that is caused by a shortage of insulin production by pancreatic cells. T2DM is the prevalent form of DM in the population and accounts for more than 85% of existing cases. Environmental factors, especially obesity and viral infections (in the case of T1DM), play a major role in the etiology of both types of diabetes[62,63,64]. In general, DM is associated with cardiovascular pathologies, which stem from hyperglycemia, a common factor in both types of DM. Epigenetic changes seen in diabetic nephropathy, such as retinopathy, neuropathy and impaired wound healing have been extensively studied to understand the etiology of the disease[65,66] (Figure No.3). Pathologies, such as diabetic retinopathy, have been shown to progress despite resolution of glycemic control, suggesting epigenetic control or metabolic memory[67,68]. Studies in mouse models of diabetic retinopathy demonstrate increased acetylation of H3K9 and increased trimethylation of H4K20. These alterations led to decreased expression of superoxide dismutase (SOD2) and retinal MnSOD, resulting in on set of diabetic retinopathy. The histone deacetylase SIRT1 is also down-regulated in hyperglycemic rats. SIRT1 is a target of miR-23b-3p, which is up-regulated in retinal endothelial cells, even in the absence of hyperglycemia[69]. Other non-coding RNAs have also been implicated in the pathology of retinopathy and nephropathy. miR-200b and miR-146a have been shown to play an important role in diabetic retinopathy[70], whereas miR-29c, miR-21, miR-200 and miR-192 have been implicated in diabetic nephropathy[71,72]. Hyperglycemia results in either DNA hypomethylation or hypermethylation in rat models of diabetes in a tissue-specific manner[73,74]. Damage to mitochondria is a distinct feature present in both diabetic retinopathy and nephropathy[75]. Diabetes

increases mitochondrial DNA (mtDNA) damage, leading to reduction in abundance of healthy mitochondria. Epigenetic modifications due to hyperglycemia affect enzymes important in mitochondrial homeostasis and thus enhance mitochondrial damage. The transport of mitochondrial transcriptional factor A (TFAM), which is essential for mtDNA replication, is also blocked in diabetes mellitus patients because of epigenetic-like modifications[76, 77].

Diabetes induces hyperglycemia that activates the reactive oxygen species (ROS) pathways causing oxidative stress. This is turn regulates epigenetic factors such as histone methyl transferases (HMTs), histone acetyl transferases (HATs), histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) to enable histone post translational modifications (HPTMs) and DNA methylation (DNA-me) leading to changes in gene expression. Persistence of these epigenetic changes may help to develop metabolic memory, which can further aggravate the oxidative stress and enable continued development of complications. Mitochondrial homeostasis is also affected by alteration in gene expression, thus enhancing mitochondrial damage resulting in chronic complications.

VIRAL INFECTIONS

Emerging viral infections pose a major threat to global public health. In 2019, COVID-19 developed into a global pandemic, which has persisted well into 2020[78]. The causative virus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) belongs to the coronavirus family, a large family of viruses that are common in humans and animals. Similar to SARS-CoV and MERS-CoV (Middle East respiratory syndrome-coronavirus), SARS-CoV-2 infects the respiratory system and has a zoonotic origin. SARS-CoV-2 may cause mild to moderate upper respiratory infections but can progress to more severe symptoms, such as bronchitis and pneumonia. A striking difference between SARS-CoV-2 and SARS-CoV and MERS-CoV is the ability to cause silent infections early on. COVID-19 can range from silent and barely symptomatic infections to critical illness[79, 80]. Viruses such as COVID-19 can spread and mutate very quickly in humans. Epigenetic studies may provide essential information to understand COVID-19 infections. In viral-host interactions, DNA-RNA methylation, chromatin remodeling and histone modifications are known to regulate and remodel host expression patterns[81]. RNA-type viruses, such as SARS-CoV-2, exhibit strong associations with internal RNA modifications. For instance, m6A, m6Am and 2′-O-me play important roles in the viral lifecycle[82, 83]. These can affect viral structure and replication, as well as the innate immune response and innate immune regulatory pathways. Viruses, such as those from the coronavirus family and influenza, are not able to make genetic modifications to their hosts; however, they can alter the epigenome, allowing them to evade the host immune response and successfully spread infection. Epigenetic mechanisms were identified as a common avenue used by MERS-CoV and H_5N_1 in "switching off" host immune responses[84]. Although DNA methylation was the primary mechanism used to suppress production of antigen presentation molecules in MERS-CoV infections, both DNA methylation and histone methylation were involved in reducing the immune response to H_5N_1. The influenza-A virus (H_3N_2) inhibits the immune response of the host by producing a protein, NS1, that mimics the tail of the histone and can interact with the host transcription complex and block antiviral gene expression in the host[85].

Studies are now ongoing to explore whether infection with the SARS-CoV-2 virus induces long-lasting immune response. A failure to induce long-term immune memory would impose serious challenges for vaccine development. Reinfection may also occur if the virus mutates enough to evade immune recognition[86]. SARS-CoV-2 particles are pleomorphic (i.e., they lack a defined structure); however, under acryoelectron microscopy, a helical nucleic acid structure is apparent. The SARS-CoV-2 genome is encoded in an enveloped positive-sense unsegmented single-strand of RNA. This RNA is directly read by ribosomes of the host cell[87]. In Figure No.4, the possible immune mechanisms present COVID-19 have been explained in detail.

1.) The virus enters the cell via interaction of the viral spike protein and receptors in the host cell-membrane. On entry into the cell, the viral genome

triggers immune response signaling in the infected cell 2.) The SARS-CoV-2 genome possesses ~14 open reading frames (ORFs) encoding approximately 27 proteins. The longest ORF is located at the 5' end of the genome and encodes 15 nonstructural proteins collectively involved in virus replication and possibly immune invasion. The 3' end of the genome encodes structural and accessory proteins. Accessory proteins are not required for virus replication or other known functions. Genbank reference genome (NC_045512.2.3) Biological changes occur in the infected cell and create interconnected double-membrane vesicles that form the replication and transcription complexes (RTCs) during SARS-CoV-2 replication. RTCs are potential antiviral targets. Immune interactions, particularly the innate immune system, are likely the driving force behind the pathogenesis of SARS-CoV-2 virus in human hosts.

The active replication and release of SARS-CoV-2 causes the host cell to undergo pyroptosis and release damage-associated molecules such as ATP, nucleic acids and ASC oligomers. These are recognized by epithelial cells and alveolar macrophages, triggering the generation of proinflammatory cytokines and chemokines, attracting monocytes, macrophages and Tcells to the site of infection and promoting further inflammation and establishing a proinflammatory feedback loop[88]. In an immune-compromised individual, this may lead to further accumulation of immune cells in the lungs, causing overproduction of pro-inflammatory cytokines, which eventually damages the lung infrastructure. The resulting cytokine storm circulates to other organs, leading to multi-organ damage. In addition, non-neutralizing antibodies produced by B-cells may enhance SARS-CoV-2 infection through antibody-dependent enhancement further exacerbating organ damage. ARDS is the primary feature of SARS-CoV-2 infection characterized by difficulty in breathing and low blood oxygen level[86,89].

The longevity of the antibody response to SARS-CoV-2 remains unknown. Most persons infected with SARS-CoV-2 display an antibody response 10 to 21 days after infection. However, detection in mild cases can take a longer time (four weeks or more), and in a small number of cases antibodies (i.e., IgM and IgG) are not detected at all within the time scale of the study. Based on the currently available data, the IgM and IgG antibodies to SARS-CoV-2 develop within 6 to 15 days post disease onset[90,91]. The median seroconversion time for total antibodies, IgM and then IgG is day-11, day-12 and day-14 post-symptom onset, respectively. The presence of antibodies was detected in <0 40% among patients within 1 week from disease onset, and rapidly increased to 100% (total antibodies), 94.3% (IgM) and 79.8% (IgG) from day-15 after onset[90]. T cell responses against the SARS-CoV-2 spike protein correlate well with IgG and IgA antibody titers in COVID-19 patients, which has important implications for vaccine design and long-term immune response[92,93]. Longitudinal serological studies that follow patient immunity over an extended period of time would be required to study the duration of immunity[94].

Two recent literatures[95,96] identified the importance of methylation pattern of the gene encoding for angiotensin converting enzyme 2 (ACE2), which is the virus receptor on host lung epithelial cells for SARS-CoV-2. It has been shown that the production rate of ACE-2 enzyme by its gene is under epigenetic control[97]. The expression of ACE2 and interferon gene depends on the methylation rate of the CpG islands in the DNA promoter sequence, which has influence on key inflammatory and immune responses in viral infections[98]. Susceptible individuals, especially men, the elderly and the smokers show a hypomethylation pattern of the ACE2 and interferon genes, whereas women, children, and nonsmokers show DNA hypermethylation and lower expression of ACE2 and interferon proteins[99-102]. High expression of interferon genes has been characterized by cytokine storm in severe SLE[103] and a cytokine storm is characteristic of SARS-CoV-2 infection[104]. The common characteristics in Lupus and SARS-CoV-2 infection are due to increased oxidative stress and DNA demethylation of ACE2. Hypomethylation and over expression of ACE-2 in T-cells will facilitate T cell viral infection and viral dissemination resulting in increased severity of COVID-19[105]. The example of cytokine storm in lupus may lead to the hypothesis that interferon-regulated genes and other inflammatory cytokine

genes are hypomethylated and thereby are epigenetically primed for transcription upon interferon exposure resulting from the viral immune response. The epigenetic priming might increase the possibility of cytokine storm in susceptible patients. We can hence get an idea to the fact that that epigenetics may play a role in delayed immune response to COVID-19 infection or ongoing inflammation after infection has been resolved[106].

LEVERAGING EPIGENETICS FOR ETIOLOGY AND DISEASE PREVENTION

Epigenomic changes are recognized as contributing to the etiology of several diseases. Thus, understanding the distribution of epigenomic markers is important in assessing the phenotype and nature of the disease. Epigenetic epidemiology deals with the relationships between the epigenomic code and disease development in a large population. The most common epigenomic modification is DNA methylation. Systematic analysis of cancer cells by Feinberg *et al*. Demonstrated large-scale deletions in heterochromatin and DNA hypomethylation over a period in several cancers. Large organized chromatin lysine modifications (LOCKs) and lamina associated domains (LADs) were further analyzed for DNA methylation changes[107,108]. Large regions of DNA, known as super-enhancers, are hypomethylated in LOCKs and LADs and this hypomethylation is preserved during further divisions, resulting in loss of expression of many of the genes in those genomic regions[109]. Differentially methylated regions are hallmark features of several cancers. The identification of these epigenetic markers would help in understanding the significance and tumor progression in different tissues[110].

Persistent exposure of cells to hyperglycemia results in epigenetic changes in the genome which are irreversible. Large-scale clinical trials have shown that diabetic patients continue to develop complications despite regaining control of blood sugar levels[111], which has been attributed to cells acquiring metabolic memory of previous hyperglycemic exposure to the cells[112]. Metabolic memory leads to a distinct epigenetic imprint that has been observed in many studies. These have shown that decrease of trimethylation at histone 3 lysine 9 serves as marker in many cases, leading to enhanced inflammation in diabetes[113,114]. This decrease of trimethylation results in suppressed expression of many of the genes such as the H3K9me3 methyltransferase (*Suv39h1*) and increased expression of the reactive oxygen species (ROS)-regulator (*p66Shc*)[115]. The lysine methyltransferase SET7 is another epigenetic marker that is functionally altered in diabetic patients and helps to sustain metabolic memory, leading to vascular dysfunction[116]. Many small-molecule inhibitors of epigenetic mediators are currently in use for treatment of diabetes. For instance, trichostatin A, suberoylanilide hydroxamic acid, MS275 and valproic acid are histone deacetylase inhibitors, whereas anacardic acid and garcinol are histone acetyl transferase inhibitors. HDAC inhibitors help in enhancement of insulin secretion, increase in insulin sensitivity, expression of anti-inflammatory genes and induction of beta cell proliferation and regeneration[117]. In addition, locked nucleic acid and antisense nucleotides against miRNAs are known to increase insulin sensitivity of cells.

Currently, we are facing a highly prolific viral outbreak. A lesson from the recent pandemic of SARS-CoV-2 is that vaccine development may take months to years. In the meantime, is it possible to influence the epigenetic regulation of multiple genes with natural interventions? The rapid dissemination of SARS-CoV-2 is a reminder of how future epigenetic studies can expand upon what we already know about these types of viruses. Specific aspects of the anti-viral response and dysregulation can be explained by epigenetics. Although epigenomic studies have found significance in understanding the progression of the disease, there is a need for more therapies based on epigenetic modifications. Manipulations of these epigenetic changes could form the basis of a therapeutic methodology by controlling viral infections and developing effective broad-spectrum antivirals[118]. A combination of genomic and epigenomic methods is required to understand the intricate changes associated with pathologies.

New advances in technology for studying the epigenetic landscape at a genome-wide scale and in a sequence-specific manner will therefore be

required to address diseases, especially rapidly emerging diseases, such as COVID-19[80]. Methylation quantitative trait loci (meQTL) is one of the techniques that has been developed to understand the epigenomic changes and subsequent alterations in the genome, which could predict for the overall health of the tissue being analyzed[110]. Epigenetic study has also proved useful in developing biomaterial-based stem cell growth models. Pluripotent stem cells isolated from various tissues can be isolated, cultured *in vitro* and differentiated into defined cell types using a combination of transcription factors and environmental cues. The exposure of these cells in hydrogel models helps understand the various interactions that decide the epigenetic changes and the ultimate cell fate[119]. These systems are increasingly being used to model and understand the genetic-epigenetic crosstalk in different pathologies[120,121]. They also have considerable potential to aid research with developing therapeutic interventions.

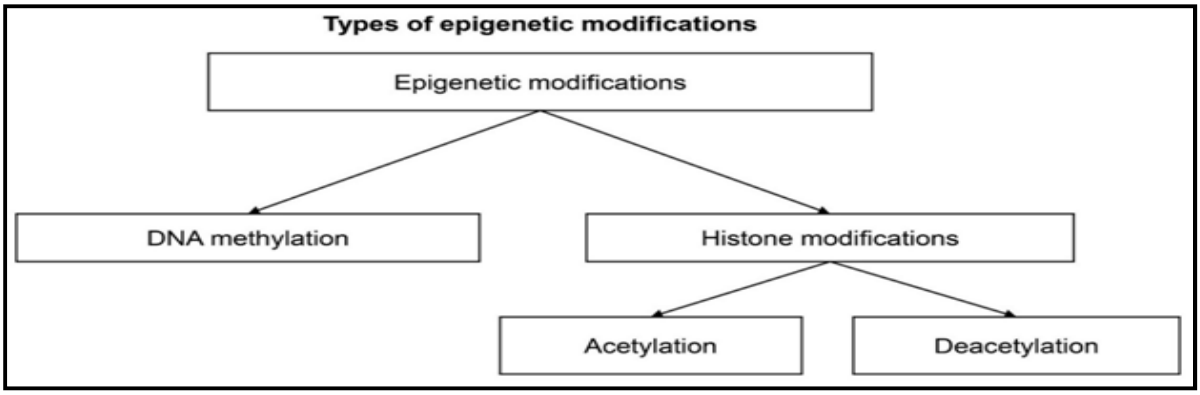

Figure No.1: Types of epigenetic modifications

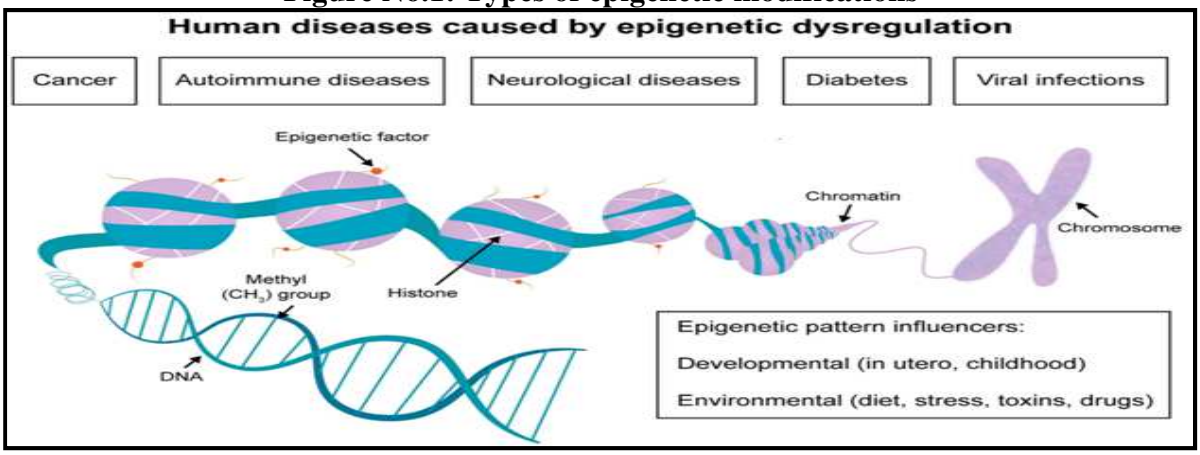

Figure No.2: Human diseases caused by epigenetic dysregulation

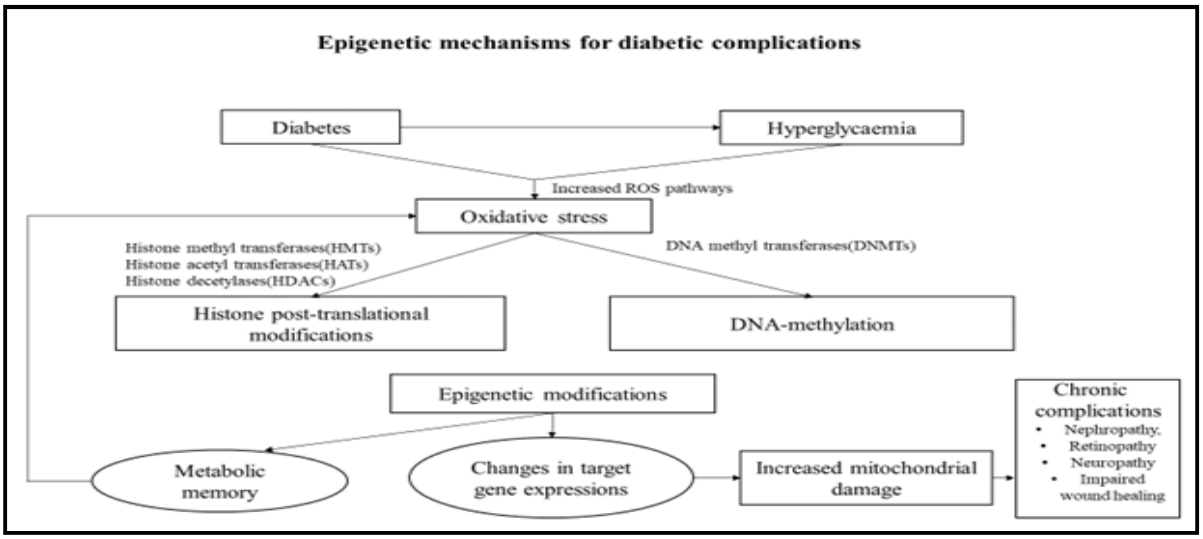

Figure No.3: Epigenetic mechanisms for diabetes complications

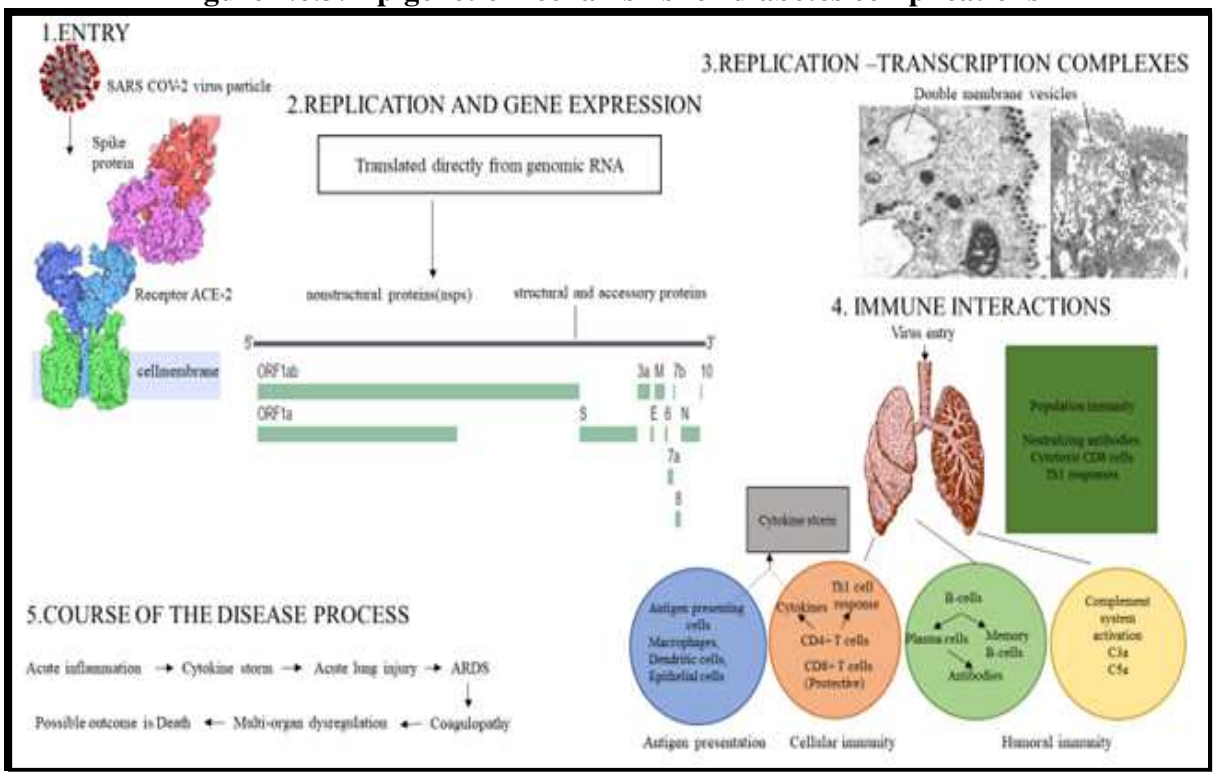

Figure No.4: The predicted antiviral immune mechanism of SARS-CoV-2

CONCLUSION

Epigenomic modifications have distinct roles to play in maintenance of stem cell pluripotency, and distinct epigenetic signatures also control tissue-specific gene expression. Understanding these epigenomic changes, both at the global and regional levels, is vital to understanding their effect on pathological conditions. Detailed study of epigenomic changes in conjunction with genomic changes is required to gain insight into the molecular mechanisms underlying human disease.

While advanced technology has aided research in the field, our understanding is impaired by the lack of high-throughput tools to study the crosstalk between genetic and epigenetic changes. Comprehensive analysis for epidemiological epigenetics needs to be done for each disease and consensus epigenomic changes need to be evaluated. Based on these observations, evaluation strategies for therapies can then be actively pursued.

ACKNOWLEDGEMENT

Special acknowledgement to Prof. Arup Ratan Bandopadhyay, Head of the Department of Anthropology, University of Calcutta for his able guidance and Prof. Britt Glaunsinger, University of California Berkley for helping in the concept development.

FINANCIAL SUPPORT AND SPONSORSHIP

Sri Sarosij Ray Memorial Research support fund.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Aditi Munmun Sengupta *et al*. Role of epigenetics in etiology and prevention of human diseases: A review based on current evidences, *Asian Journal of Research in Biological and Pharmaceutical Sciences,* 8(3), 2020, 85-100.