

REVIEW ARTICLE

Epigenetics: A possible answer to the undeciphered etiopathogenesis and behavior of oral lesions

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ABSTRACT

Much controversy has existed over the etiopathogenesis and management of oral lesions, especially oral malignancies. The knowledge of genetic basis is proving to be inadequate in the light of emerging new mechanisms termed epigenetic phenomena. The present review article aims to understand the role of epigenetic mechanisms in oral lesions. Epigenetics is the study of acquired changes in chromatin structure that arise independently of a change in the underlying deoxyribonucleic acid (DNA) nucleotide sequence. Key components involved in epigenetic regulation are DNA methylation, histone modifications and modifications in micro ribonucleic acids (miRNA). Epigenetics is a reversible system that can be affected by various environmental factors such as diet, drugs, mental stress, physical activity and addictive substances such as tobacco, nicotine and alcohol. Epigenetics may also play a role in explaining the etiopathogenesis of developmental anomalies, genetic defects, cancer as well as substance addiction (tobacco, cigarette and alcohol). Epigenetic modifications may contribute to aberrant epigenetic mechanisms seen in oral precancers and cancers. In the near future, epigenetic variations found in oral dysplastic cells can act as a molecular fingerprint for malignancies. The literature in English language was searched and a structured scientific review and meta-analysis of scientific publications from the year 2000 to year 2015 was carried out from various journals. It was observed that epigenetic marks can prove to be novel markers for early diagnosis, prognosis and treatment of oral cancers as well as other oral diseases.

Key words: Deoxyribonucleic acid (DNA) methylation, Epigenome, histone modification, micro-ribonucleic acid (miRNAs), oral cancer, small interfering ribonucleic acids (siRNAs)

INTRODUCTION

Despite enormous research in the fields of diagnosis and management of oral premalignancies and malignancies; their etiopathogenesis and behavior have long been a matter of discussion, debate and controversy and not many advancements have been possible in managing these lesions. Oral malignancies are still graded based on the tumor/node/metastasis staging and despite extensive research, no functional classification based on histopathological typing or molecular profiling is presently being used at cancer

management centers and hospitals. Another matter of debate has been the fact that an increasing number of cases of oral premalignancies and malignancies are not related to any deleterious habits, which questions their etiopathogenesis that is commonly related to habits such as chewing of tobacco and its products, areca nut usage, cigarette smoking and alcohol consumption. Over the years, the treatment approach for oral malignancies has remained constant. Excision and removal of the tumor usually remain the only choices for management

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and most specialists still feel handicapped at actually treating the tumor or preventing its recurrence. Another aspect of the etiopathogenesis of orofacial neoplasms has been their genetic basis. Much of the research at the genetic level has been carried out on chromosomal mutations and other genetic defects, but even this has not helped in achieving pinpoint diagnosis or prompt treatment in most cases of oral malignancies. This has led to speculations about the role of phenomena other than genetic events, which have been termed “Epigenetics.” In the past few years, many researchers have made attempts to decipher these internal mechanisms and have postulated the rectification of these mechanisms, when they appear aberrant, for possible management of the oral diseases and malignancies. This has been authenticated by evidence showing inter-generational exchange of genetic information by the genome, by mechanisms other than its basic genetic material.

Epigenetic changes have been described as stable but potentially reversible alterations in a cell’s genetic information that result in changes in gene expression but do not involve changes in the underlying deoxyribonucleic acid (DNA) sequence.^[1-3] Some changes that may occur in the lifetime of the parent may in turn affect the phenotype of their offspring, leading to an epigenetic phenomenon that is transgenerational.^[4] The concept of epigenes (transposable elements in our genes) as factors travelling with the genes between generations is becoming increasingly popular. Various factors have been identified in the environment, diet and habits of an individual which affect not only the person but also subsequent generations.^[5] Epigenetic modifications cause remodelling of the chromatin which results in activation or inactivation of a gene, thus contributing to the development of diseases including malignancies.^[6] Three key mechanisms involved in epigenetic regulation have been identified, namely DNA modifications, histone modifications and ribonucleic acid (RNA) modifications. Although epigenetics and genetics are individual and distinct fields, potential interactions have been observed to occur between them. Epigenetic marks may influence genetic changes such as mutation, transposition and recombination of DNA sequence and the predisposition of a gene to be selected for epigenetic changes. Furthermore, the mechanisms enabling epigenetic effects are themselves subject to evolution.^[4] Hence, the present review was done to understand the evolution and concepts of epigenetics and to understand its significance in relation to oral lesions, especially oral cancer.

To understand the role of epigenetic mechanisms in oral lesions, especially oral malignancies, the literature in English language was searched and a structured scientific review and meta-analysis of scientific publications from the year 2000 to 2015 was carried out from various journals using search engines such as PubMed, Wiley, Google Scholar, Science Direct and EBSCO host. The keywords Oral cancer, Epigenetics, DNA methylation, Histone modification, miRNA, small interfering

RNAs (siRNA), tobacco, cigarette, alcohol, oral rinses and buccal swabs were used for the search.

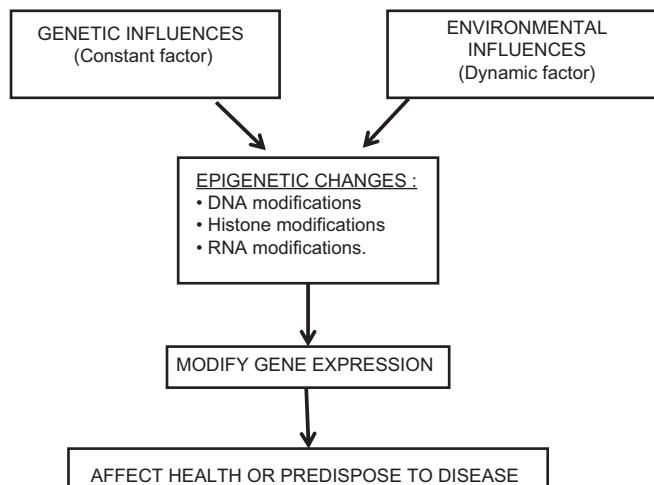
For a long time, environmental and genetic factors were thought to be independent mechanisms, but recent evidence suggests that epigenetics bridges these two factors.^[7] The term epigenetics was coined by Waddington in the 20th century and he hypothesized that patterns of gene expression define each cell type, turning genes on and off, thus linking genes to development.^[8-11] Table 1^[12-16] provides a brief description of the historical perspective of epigenetics. Genetic and epigenetic mechanisms are very closely related. Yet, there are many important differences between the two systems. Unlike genetic changes, epigenetic changes do not depend on DNA sequence changes but depend on modifications of the DNA, other than those involving the basic sequence of adenine, guanine, cytosine and thymine nucleotides.^[3] Genetic changes are stable and can rarely be reversed, whereas epigenetic changes are often reversible.^[3,10] The genotype is constant except for changes caused by mutagens and there is no inheritance of acquired characteristics, whereas the epigenetic process is dynamic and changes in response to diseases and environmental factors.^[6,10] In contrast to genetic changes which usually involve a single gene, epigenetic modifications involve more than one gene.^[2,17-19] Epigenetic mechanisms that modify chromatin structure can be divided into three main categories: DNA modifications, histone modifications and modifications of noncoding RNAs (ncRNAs). These modifications work together to regulate the functioning of the genome by regulating the dynamics of chromatin.^[9] Flowchart 1 helps to understand the mechanism by which epigenetic phenomena function.

The first evidence that DNA methylation or demethylation might have an important biological role was provided by Griffith and Mahler in 1969.^[10] Currently, DNA methylation is the most studied epigenetic mechanism.^[20] Studies have shown that DNA methylation provides a stable gene silencing mechanism that plays an important role in regulating gene expression and chromatin architecture.^[2,5,9,21] The DNA can be modified by the addition of methyl groups to specific DNA sequences with cytosine and guanine bases separated by a phosphate molecule (CpG islands).^[6,20] X-chromosome inactivation (XCI) and imprinted genes are classic examples of naturally occurring CpG island methylation during development.^[9,22] This process of DNA methylation is regulated by DNA methyltransferases (DNMTs). Presently, five DNMTs have been identified: Dnmt1, Dnmt2, Dnmt3a, Dnmt3b and DnmtL.^[15,23,24] There is strong evidence that DNA methylation can provide a primary switch for epigenetics.^[10] Loss of DNA methylation is related to increased risk of tumors due to chromosomal instability. It has been considered as the earliest epigenetic change from a normal cell to a premalignant cell.^[8]

The DNA is wrapped around a histone core to form the nucleosome, which forms the fundamental unit of the

Table 1: Historical events in epigenetics

Year	Events
Early twentieth century	C.H Waddington suggested that genetics and developmental biology were related ^[12,-14]
1942	Term “epigenetics” was coined from Greek work “epigenesis” by C.H Waddington ^[13,15,16]
1958	Nanney gave the concept of genetic and paragenetic systems ^[12,13,16]
1960	The concept of epigenetics in molecular and cellular biology started to coexist ^[14-16]
1968	Markert proposed that there is no gene coding for cancer and that normal gene activity is misprogrammed by epigenetic mechanisms to produce a neoplastic activity ^[12,16]
1993	Herring defined epigenetics as “the entire series of interactions among cells and cell products which leads to morphogenesis and differentiation” ^[12,13,16]
1996	Lars Bygren and Marcus Pembrey were amongst the first scientists to start work on epigenetics in humans ^[12,13,15]
2006	Pembrey and Bygren found sex-specific, male-line transgenerational responses in humans ^[14,15]
2007	Feinberg discussed the idea that epigenetic modifications may play a role in cancer predisposition, and that such changes should be considered as targets for preventive oncology ^[12,13,15]
2008	Park <i>et al.</i> were able to reprogram somatic human cells to a pluripotent state, using a reversal of differentiation, which resulted in significant epigenetic remodeling ^[15,16]
2009	Gabory <i>et al.</i> proposed that environmental factors may induce epigenetic changes via three possible mechanistic pathways Activation/inhibition of chromatin machinery Activation of nuclear receptor by ligands Membrane receptor signaling cascades ^[12,13,16]
2010	Pregnant women in their last trimester at the time of the attacks on the Twin Towers and suffering from posttraumatic stress disorder were observed to have children born with similar manifestations ^[14-16]
2012	England’s Avon longitudinal study of parents and children gave strong hints in favor of epigenetic mechanisms ^[12,16]
2014	Langevin <i>et al.</i> reported that novel DNA methylation targets in oral rinse samples could predict survival of patients with oral squamous cell carcinoma ^[12,13]



Flowchart 1: Epigenetic phenomena

chromatin. These histone proteins are themselves subject to reversible epigenetic modifications by processes such as methylation, acetylation, phosphorylation, biotinylation, ubiquitination, sumoylation and adenosine diphosphate ribosylation which occur at the N-terminal tails of histones and regulate important cellular processes such as transcription, replication and repair.^[2,5,21,25] The most studied histone modifications are methylation, acetylation and phosphorylation. These modifications are mediated by enzymes such as histone methyltransferases, histone demethylases, histone acetyltransferases, histone deacetylases, histone phosphorylases and histone phosphatases.^[2,5,6,24-26] The combined effect of all

these modifications has been termed “histone crosstalk.”^[23] Histone modifications can lead to either activation of the genes (associated with a loosely packed chromatin) or inactivation of the genes (associated with a compact chromatin). These histone modifications are proposed to play a key role in determining cellular identity.^[6,9] Of late, various potential roles of histone proteins have been postulated which include uses such as prognostic biomarkers in the detection of aggressive behavior of tumors as well as a predictive factor of chemotherapy and radiotherapy response.^[5,10,22]

Along with changes in the DNA and supporting histone framework, certain RNA modifications have also been proposed to cause epigenetic changes. These mainly occur in the ncRNAs that are classified according to their size as a first group of small ncRNAs, which include siRNAs and P-element induced wimpy testis-interacting RNAs and a second group of micro RNAs (miRNAs).^[27] miRNAs play an essential role in modifying gene expression as well as in controlling DNA methylation and histone modifications. They can function as both oncogenes and tumor suppressors genes and can regulate target genes with important functions in carcinogenesis such as TPM1, PTEN and bcl-2.^[5,15,28] miRNA profiles can also be used to classify human cancers.^[2,16] Recently, much work has been carried out on the role of miR-21, miR-345 and miR-181b in oral cancer progression.^[28] siRNAs are a class of short, double-stranded RNAs which are involved in the RNA interference (RNAi) pathway and suppress the expression of specific genes. They have been shown to be involved in both

DNA methylation and histone modifications.^[2,19] All these mechanisms of DNA, histone and RNA modifications are closely interrelated and are responsible for regulating gene expression in the healthy cells as well as may instigate aberrant gene expressions in cancer cells. Much lesser investigated epigenetic mechanisms include small regulatory RNA molecules, non-covalent mechanisms (such as nucleosome remodeling and replacement of canonical histone proteins with specialized histone variants), self-sustaining loops and structural inheritance.^[4,9,10]

Various factors can provoke epigenetic changes. These may be physiological or pathological. Epigenetic changes increase during life and age itself may be a risk factor for epigenetic changes. Studies have proved that the mother's diet influences fetal development as well as affects the offspring as an adult. Several nutritional factors such as folate, Vitamin B12, Vitamin A, methionine, choline, betaine, biotin, niacin, pantothenic acid and zinc as well as bioactive dietary components (genistein and polyphenols) may result in epigenetic modifications, which in turn participate in events such as embryonic development, aging and carcinogenesis.^[3,6,21] The epigenome may be especially plastic during early development of the individual and is susceptible to modifications. Thus, intervention at this stage can provide a therapeutic advantage.^[22]

Significant effects of various habits have been found in relation to epigenetic changes.^[25,26] Long-term epigenetic changes in the DNA have been found in smokers.^[11] In actively drinking individuals, increased levels of homocysteine have been found, which plays an important role in DNA methylation.^[15,17] In squamous cell carcinoma of the head and neck, alcohol has been also found to be associated with changes in the methylation pattern.^[6]

Epigenetics can play a role in health as well as disease. Role of various bacteria and viruses has been implicated in epigenetic mechanisms. Bacteria-induced epigenetic deregulations may affect host cell function either to promote host defense or to allow pathogen persistence.^[29] Pathogens in the oral mucosa may cause epigenetic changes in the host, which may, in turn, influence the progression of disease or cancer. In patients with squamous cell carcinoma of the head and neck region, bacteria were shown to be associated with methylation of the multidrug resistance gene and increase in methylation in the E-cadherin gene after *Helicobacter pylori* stimulation was also observed.^[5,6] Virus-induced epigenetic changes include changes due to chronic human immunodeficiency virus (HIV) infection that has revealed epigenetic changes in key genes. Studies have recently found an association between poorly differentiated head and neck squamous cell carcinoma and human papillomavirus-16. The bacterial pathogens that cause periodontal diseases are known to cause epigenetic modifications to the genomes of Epstein-Barr virus, Kaposi sarcoma-associated herpes virus and HIV, which may be

of significance for understanding the etiopathogenesis of virus-associated malignancies.^[30,31]

Development of oral cancer is a multistep process involving an accumulation of genetic and epigenetic alterations resulting in cellular dysregulation and uncontrolled growth.^[32] Markert has stated that normal gene activity is misprogrammed by epigenetic mechanisms to produce a neoplastic pattern of metabolism in which all of the individual components are normal.^[3] Cellular aging and chronic inflammation may be potential inducers of epigenetic alterations in oral mucosal cells.^[5] Epimutations can lead to silencing of tumor suppressor genes independently and also in conjunction with deleterious genetic mutations or deletions; thus, serving as the second hit in the "two-hit" model of carcinogenesis proposed by Knudson. Hypermethylation and consequent silencing of several tumor suppressor genes have been identified in oral cancers. The genes found hypermethylated include cell cycle control genes (p16, p15), apoptosis genes (p14, DAPK, p73 and RASSF1A), Wnt signaling genes (APC, WIF1, RUNX3), cell-cell adhesion genes (E-cadherin), DNA-repair genes (MGMT, BRCA1 and hMLH1), tumor suppressor genes (p16, MLH1, BRCA1, *CDKN2A*, *pRB*, *APC*, *PTEN*, *BRCA1*, *VHL* and *CDH1*), metastasis-related genes, hormone receptor genes and genes inhibiting angiogenesis.^[9,33-36] The tumor microenvironment may itself be viewed as an epigenetic modifier with the potential to promote or prevent malignant outgrowth.^[36] Multiple factors and mechanisms have been discovered which have a potential role in carcinogenesis. These include loss of imprinting; E-cadherin hypermethylation; reduced expression of the enzyme death associated protein kinase; hypermethylation of genes p14, p15, p16; DNA methylation in the promoter region is deleted in colorectal cancer (DCC) gene; hypermethylation of MINT 1 and MINT 31 and epigenetic deregulation of Notch signaling.^[9,15,35-37] Methylated genes in tumors identified in recent investigations in head and neck squamous cell carcinoma such as HOXA9, HS3ST2, NPY, EYA4 and WT1 have been suggested as biomarkers for early detection of oral cancers.^[37] Studies have reported using methylation-specific polymerase chain reaction in oral rinses and found that hypermethylation status of circulating DNA could be used as a tumor marker to monitor patients with premalignant and malignant oral lesions. Other studies have identified up to seven novel DNA methylation markers in oral rinse samples from oral cancer patients.^[32] Epigenetic modifications are tissue specific and DNA from oral rinses, buccal swabs or whole saliva could be used for determining the epigenetic status of oral tissues.^[6,38] miRNA levels have also been found to be differentially expressed in oral squamous cell carcinoma tissues, serum and saliva. These can provide biomarkers for early diagnosis of oral squamous cell carcinoma. They can also serve as a potential biomarkers of nutritional status in humans.^[1,5,33] Diseases caused by the expression of a dominant gene can be treated by ligand-targeted nanoparticles for siRNA.^[5,21] Various studies

have demonstrated the possibility to detect hypermethylation in saliva. Biomarkers based on the methylation profile evaluation in exfoliated mucosa cell samples could represent a powerful class of minimally invasive markers for squamous cell carcinoma detection.^[1,25,26,33,39]

Epigenetics has provided a new dimension to clinical genetics. Epigenetic dysregulation in diseases is increasingly being studied as a potential mediator of pathophysiology of various diseases and malignancies.^[40-42] In recent years, epigenetics has become an emerging mechanism in the etiology of diseases such as Type 2 diabetes mellitus, obesity, inflammation, neurocognitive disorders, cardiovascular diseases, neurodegenerative

diseases and immune diseases.^[18,21,43,44] X-inactivation and imprinting are the other major types of epigenetic events that occur in cancer. Several diseases and syndromes occur with abnormal DNA methylation or imprinted gene sites including Silver–Russell syndrome, Beckwith–Wiedemann syndrome, Angelman syndrome, Prader–Willi syndrome, Williams syndrome, Di George–Velocardiofacial syndrome, Fragile X syndrome, autism, schizophrenia, Rett’s syndrome and XCI disorders such as Ring Turner syndrome.^[3,8,39,41,45] Epigenetic alterations are currently used clinically as diagnostic markers of various diseases.^[29,41,46] Table 2 gives a brief description of how epigenetics affects oral health and its role in causing oral lesions.

Table 2: Orofacial pathologies linked to epigenetics

Epigenetic change	Pathology
Long term hypomethylation and hypermethylation of DNA caused by smoking	HNSCC ^[27]
Increased levels of homocysteine causing DNA methylation caused by alcohol intake	HNSCC ^[10,22,27]
Bacteria act as epimutagens and leave an epigenetic memory called bacterial imprints	Bacterial infections and autoimmune diseases ^[2]
Methylation of multidrug resistance gene by bacteria	HNSCC ^[6]
Human papilloma virus-16 induced changes	Associated with poorly differentiated squamous cell carcinoma ^[2]
Epigenetic modifications caused by EBV, Kaposi’s sarcoma-associated herpes virus, HIV	Associated with periodontal disease ^[2]
EBV, HIV, HSV as epimutagens	Virus associated malignancies ^[2,8]
Hypermethylation and consequent silencing of cell cycle control genes, apoptosis genes, Wnt signaling genes, cell-cell adhesion genes, DNA-repair genes, tumor suppressor genes, metastasis-related genes, hormone receptor genes and genes inhibiting angiogenesis	HNSCC ^[1,6]
<i>E-cadherin</i> hypermethylation	Adverse histological grade and poor survival in oral squamous cell carcinoma. Expression has also been highly correlated with regional metastasis ^[9]
Reduced expression of the enzyme death associated protein kinase	HNSCC. Correlation with nodal stage is under investigation ^[9]
Deregulation and widespread changes occur in miRNA expression during tumorigenesis	miRNAs can function as either tumor suppressors or oncogenes in HNSCC depending upon their target genes ^[21]
p14, p15, p16 promoter hypermethylation	HNSCC. predict malignant transformation ^[27,4]
DNA methylation in the promoter region of deleted in colorectal cancer	Significant correlation with mandibular invasion in oral cancer ^[9]
Hypermethylation at MINT 1 and MINT 31 genes	Significant correlation with poor survival in oral cancers ^[9]
Methylated genes in HOXA9, HS3ST2 and NPY	HNSCC ^[9,21]
Epigenetic deregulation of Notch signaling	HNSCC. Can signal recurrence ^[14,27]
miRNA levels differentially expressed	HNSCC. Indicate metastatic disease ^[9]
Changes in siRNA	Autosomal dominant diseases ^[4]
Oral microflora and local biofilm may create an epigenetic footprint in the oral mucosa and periodontal tissues	Modification of the local inflammatory response and oncogenic potential ^[2,4]
Loss of imprinting of a tumor-related gene	HNSCC ^[9]
Abnormal DNA methylation or imprinted gene sites	Silver-Russell syndrome, Beckwith–Wiedemann syndrome, Angelman syndrome, Prader-Willi syndrome, Williams syndrome, Di George-VCFS, Fragile X syndrome, Rett syndrome, Ring Turner syndrome ^[35]
Promoter hypermethylation present in histologically negative margins in carcinoma cases	Useful molecular marker for predicting overall survival in HNSCC ^[14]

EBV: Epstein–Barr virus, HIV: Human immunodeficiency virus, MINT: Methylated in tumor, miRNA: Micro RNA, siRNA: Small interfering RNA, HNSCC: Head and neck squamous cell carcinoma, VCFS: Velocardiofacial syndrome

Factors in the diet such as retinoids have been shown to suppress carcinogenesis in a variety of epithelial tissues including skin and oral mucosa.^[5] Certain natural compounds such as sulforaphane found in cruciferous vegetables, compounds from garlic and grapes, genistein and curcumin have been found to alter epigenetic patterns.^[6,21] Epigenetic changes can be exploited for therapeutic intervention, which is authenticated by the recent Food and Drug Administration on approval of three epigenetic drugs for cancer treatment.^[9,23,34,36,39,47,48]

The concept of inherited epigenetic susceptibility to tobacco-related cancers can be used for identification of susceptible individuals to allow more focused prevention strategies in oral cancers. The cell cycle regulator p15 predicts malignant transformation and has been targeted.^[35] Various tests have been generated and devised to understand epigenetic information. These include a single gene-based DNA methylation assay, a microarray-based epigenomic assay and a high-density bead chip-based epigenomic assay.^[22,41] Recent sequencing technology has revealed the presence of copy-number variations, which are associated with susceptibility to common diseases.^[41] Currently, several epigenetic drugs are being tested in clinical trials or are already being used.^[18,22,36] Development of several small molecule inhibitors such as SGI-1027, RG-108 and MG-98 has provided nonnucleoside compounds, which can effectively inhibit DNA methylation without being incorporated into the DNA.^[49] Several pathways appear to be specifically epigenetically deregulated in the cases showing greatest biological aggression that often prove refractory to aggressive conventional therapies, emphasizing the need for epigenetic biomarker panels.^[33]

The rapidly evolving field of epigenetics is contributing to our understanding of gene-environment interactions. The future appears bright if the knowledge of epigenetic phenomena can be utilized for deriving diagnostic, therapeutic and prognostic information about oral malignancies and also other oral diseases.^[35,50] Hypermethylation of oncogene promoters in oral mucosal cells can serve as a molecular fingerprint which can be very helpful in diagnosis as well as classification of malignancies. Revealing hypermethylation present in histologically negative margins in carcinoma cases could be a useful molecular marker for predicting the overall survival of the patient.^[5] Spreading awareness about epigenetic mechanisms and their role in health could encourage a more balanced lifestyle, discouraging any deleterious habits in individuals.^[42,51,52]

Presently, many studies are being undertaken to understand epigenetic mechanisms better in both health and disease. Studies from northern Sweden show an association between the childhood food supply of the father or the paternal grandparents and the offspring's longevity or risk of diabetic or cardiovascular mortality. A contemporary United Kingdom cohort study also shows an association between paternal onset

of smoking in mid-childhood and increased body mass index in their future sons. Similarly, a contemporary population from Taiwan shows an association between paternal betel nut chewing and early onset of the metabolic syndrome in the offspring. The sequencing of the human genome is being followed by the epigenome project, which will eventually unravel the significance of the field of epigenetics.^[3,22]

CONCLUSION

Presently, much research is going on in the field of epigenetics. Epigenetic marks can provide new insights in the early diagnosis, prognosis and treatment of oral precancers, cancers and various other oral diseases. DNA from oral rinses and buccal swabs can serve as a routinely used noninvasive tool that can be employed for screening for epigenetic alterations in oral tissues. In addition, epigenetics can be utilized for the development of novel therapeutic interventions for various developmental diseases as well as for addiction. Thus, epigenetic therapy is now a reality that can change our future for good. The change in our genes has been impossible, but the change in our epigenes now appears possible!

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