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RESEARCH ARTICLE

EPIGENETICS IN ORAL PATHOLOGY

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Abstract

Epigenetics is a major turn away from molecular biology. It helps us understand the biological phenotype that arises from the interaction of the human genome with the environment in health and in disease. Epigenetic mechanisms such as DNA methylation, histone modifications and RNA interference have been shown to silence key genes involved in cell proliferation, differentiation and genome integrity, and clearly have a central role in oral cancer. Here, we describe the basics of epigenetics, its role in physiological and pathological events in oral cavity.

Introduction:-

"It is estimated that the human body contains about 50 trillion cells - which works out to 100 trillion meters of DNA per human. This means that each of us has enough DNA to go from here to the Sun and back more than 300 times." Annunziato, A. (2008) DNA Packaging: Nucleosomes and Chromatin. Nature Education 1(1):26

Genes are segments of deoxyribonucleic acid (DNA) that has the code for a specific protein that functions in one or more types of cells in the body. Chromosomes are structures within cells that contain a person's genes. The genotype (or genome) is a person's unique combination of genes or genetic makeup. Thus, the genotype is a complete set of instructions on how that person's body synthesizes proteins and thus how that body is supposed to be built and function. Where as the phenotype is the actual structure and function of a person's body.

The structure of DNA:

Chromosomal DNA has a distinct and complex structure and is packaged inside microscopic nuclei with the help of Histones. They are positively charged proteins that strongly adhere to negatively charged DNA and form complexes called Nucleosome. It is the basic unit of DNA packaging consisting of a segment of DNA wound around a core "octamer" of 8 histone proteins (two each of histones H2A, H2B, H3, and H4). **Figure 1,2**

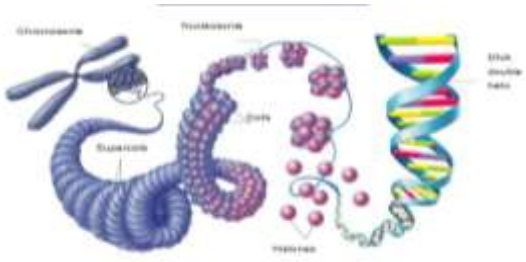

Figure 1:-

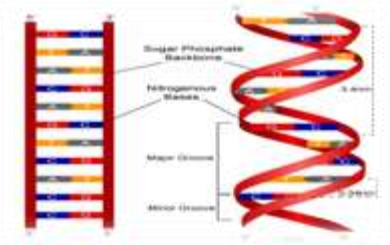

Figure 2:-

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Epigenetics:

Epigenetics, in a broad sense, is a bridge between genotype and phenotype. It is a phenomenon that changes the final outcome of a locus or chromosome without changing the underlying DNA sequence. Epigenetics describes changes in the genome that influence the gene expression without altering the DNA sequence. It is the chemical alterations in the DNA and its associated histone proteins where remodeling/re-organization of the chromatin occurs. The Greek prefix "epi" in epigenetics means "on the top" or "in addition to" genetics.[1] So, Epigenetics refers to stable alterations in gene expression with no underlying modifications in the genetic sequence, rather altering chemical structure of DNA and is best exemplified by differentiation, in which multiple cell types diverge physiologically despite a common genetic code.

History:

C.H.Waddington has defined Epigenetics as; 'The casual interactions between genes and their products, which bring the phenotype into being'. In 1957, he proposed the concept of an epigenetic landscape to represent the process of cellular decision-making during development. At various points in this dynamic visual metaphor, the cell (represented by a ball) can take specific permitted trajectories, leading to different outcomes or cell fates. Figure reprinted from Waddington, 1957. (**FIGURE 3** Epigenetic landscape to represent the process of cellular decision-making during development)[1]

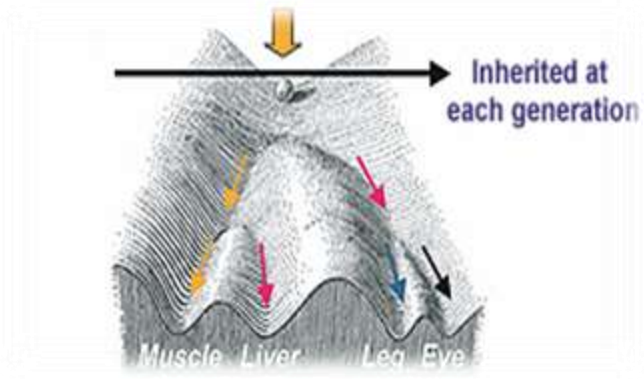


Figure 3:-

According to **Herring** (1993); "The entire series of interactions among cells and cell products which leads to morphogenesis and differentiation." **Berger et al**. (2009) defined it as "A mitotically (or meiotically) inheritable change in gene expression, independent of an alteration in DNA sequence". According to **Russo et al**., epigenetics was defined as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in the DNA sequence." A consensual definition of epigenetics is described as follows "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence." [1,2] Another definition was proposed by Adrian Bird as "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states."[3]

Table 1:- Historical Events In Epigenetics.

Early 20th century	C.H Waddington : relation b/w genetics and developmental biology ("epigenesis")
1942	"epigenetics - definition"
1948	Methylated cytosine was first detected in a preparation of calf thymus by Rollin Hotchkiss at the Rockefeller Institute of Medical Research, New York.
1958	Nanney - genetic and paragenetic system
1960	The concept of epigenetics in molecular and cellular biology started to coexist
1964	Allfrey *et al*. first reported histone acetylation
1968	Markert - Normal gene activity is misprogrammed by epigenetic mechanisms to produce a

	neoplastic activity
1993	Herring : definition , Number of cancer drugs have been developed to inhibit DNA methylation. The first such drug was Azacytidine (Vidaza). This was licensed by the FDA in 2004 for the treatment of blood cancers. Its approval marked a major milestone in the development of epigenetic cancer therapy
1995	First evidence published to demonstrate reduced DNA methylation contributes to formation of tumours
1999	First evidence from mammals that epigenetic changes can be passed down generations
2004	FDA approved first DNA methylation inhibitor drug, azacitidine (Vidaza®), for treatment of rare bone marrow disorder
2006	FDA approved second DNA methylation inhibitior, decatabine (Dacogen)
2007	Feinberg : epigenetic modifications may play a role in cancer predisposition
2009	Gabory et al. : Environmental factors may induce epigenetic changes
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
2012	Transgenerational epigenetic phenomenon
2014	Langevin et al - DNA methylation - predict survival of patients with oral squamous cell carcinoma.
2015	Chinese regulatory authorities approved Chidamide, a histone deactylase inhibitor, for peripheral T cell lymphoma
2015	Experiments with mice showed that azacytidine treatment enhanced the responsiveness of tumors to anti–CTLA-4 therapy

Genetics and epigenetics has major variations that it should be clearly understood.[4]

Table 2:- Differences between genetic and epigenetic changes.

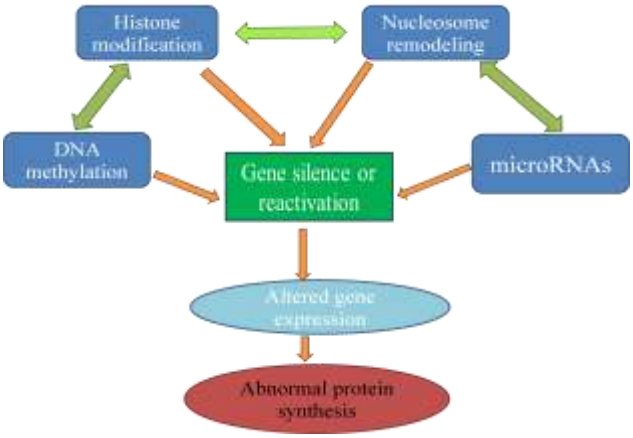
GENETIC CHANGES	EPIGENETIC CHANGES
Depend on DNA sequence changes	Modifications of the DNA
Genotype is constant and no inheritance of acquired characteristics	Changes in response to diseases and environmental factors
Stable & rarely be reversed	Dynamic and often reversible
Involve a single gene	Involve more than one gene
Genetics is based on cell lineages and clonal Inheritance	Not depended on clonal inheritance
The organism starts as a single cell, and ends up as a clone of cells.	Epigenetic changes often occur in groups of cells, for example, the induction of muscle tissue in mesoderm cells.
Environmental influences do not change the genotype (leaving aside mutagens)	Normal development Depends on communication between cells.

Epigenetic Mechanisms

Epigenetic mechanisms exert an additional layer of transcriptional control that regulates gene expression. They are coupled and interact to modify chromatin structure and function. They occur throughout the lifetime of the organism, beginning in intrauterine environment, and accumulate in tissues and cells over time to modify gene expression patterns and cellular phenotypes[3]

There are three categories of signals that culminate in the establishment of a stably heritable epigenetic state: a signal that we propose to call the ''Epigenator,'' which emanates from the environment and triggers an intracellular pathway; an ''Epigenetic Initiator'' signal, which responds to the Epigenator and is necessary to define the precise location of the epigenetic chromatin environment; and an ''Epigenetic Maintainer'' signal, which sustains the chromatin environment in the first and subsequent generations. [4]

3 major events in epigenetics are: **(figure 4)**



- **a) DNA methylation**
  - **Hypermethylation**
    - **Global**
    - **CpG**
  - **Hypomethylation**
- **b) Histone modification**
  - **Acetylation**
  - **Methylation**
  - **Phosphorylation**
  - **Ubiquitination**
  - **Sumoylation**
- **c) RNA interference.**
  - **SiRNA**
  - **miRNA**
  - **non coding RNA**

DNA Methylation:

The first suggestion that DNA methylation (or demethylation) might have an important biological role was made by Griffith and Mahler, who proposed in 1969 that it could provide a basis for long term memory in the brain. [5] It is the most studied mechanism, being responsible for gene silencing and chromatin architecture. DNA methylation primarily materializes within the so-called "CpG islands" that are composed of a series of CpG dinucleotide structures located usually at the 5′ end of genes. The CpG dinucleotides can also be found in genome regions that contain repetitive sequences, such as in the case of retrotransposon elements, rDNA, and centromeric repeats.[6,7,8] While most of the CpG sites within repetitive sequences are methylated, in the case of the grouped ones (CpG islands) that usually occupy more than half of the promoter of a certain gene, the pattern is consistently unmethylated for both undifferentiated and differentiated tissues.[9] CpG islands most of which are unmethylated all

times in normal cells, can acquire methylation under special developmental circumstances or in abnormal cells (permanent cell lines or cancer cells). It is clear, however, that not all regions of the genome are equally accessible to DNA methyltransferases.[6] Most of the CpG dinucleotides in mammals are methylated. However, regions in genome with high frequency of CpG dinucleotides, called CpG islands, reside in or near promoters of housekeeping genes and are unmethylated. DNA methylation is transmitted through mitosis and controls gene function by inhibiting DNA transcription. The latter is achieved by two ways. First, DNA methylation prevents transcription factors from binding to gene promoter and, second, methyl-CpG groups bind proteins, namely methyl-CpG-binding domain proteins (MeCPs), which, in turn, recruit histone-modifying proteins leading to chromatin inactivation.[10]

Some isolated cases also show methylated CpG islands, eg; in the case of the X-chromosome that is inactivated during development and also for some genes associated with incipient development stages that are silenced through methylation in adult tissues. Methylation is catalyzed by DNA methyltransferase enzymes that use s-adenosyl-methionine (SAM) as a methyl donor to replace a hydrogen atom with a methyl group at the carbon 5 position of the cytosine pyrimidine ring. This only occurs at cytosine bases located 5′ to a guanosine in a CpG dinucleotide. DNA methylation is regulated by a family of DNMTs: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. DNMT1 preferentially methylates hemimethylated DNA in vitro and is localized to replication foci during S phase. As such, it is the proposed maintenance methyltransferase responsible for copying DNA methylation patterns to the daughter strands during DNA replication. DNMT3A and DNMT3B, in contrast to DNMT1, have preference for unmethylated CpG dinucleotides and perform de novo methylation during development.[11]

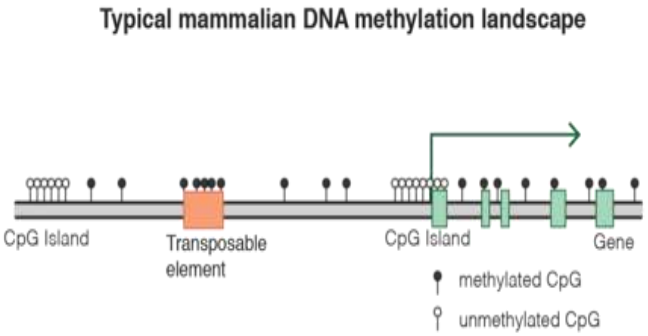


Figure 5:-

There are three main mechanisms which link methylation to cancer: transcriptional silencing via hypermethylation in the promoter regions of tumour suppressor genes, hypomethylation (demethylation) resulting in the failure to repress expression of tissue restricted or proto-oncogenes and genome wide hypomethylation leading to increased mutation rates and chromosome instability. Most CpG islands are located at the promoter regions of genes and are unmethylated in normal cells. Hypermethylation of these regions causes altered transcription or "silencing" of the target gene. This may be a natural event, for example fully methylated islands are associated with many silent genes on the inactive X chromosome in females.[12]

Histone modification:

In eukaryotic cells, DNA is wrapped around an octameric histone core to form the nucleosome, the fundamental subunit of chromatin. Many residues in the histone proteins are subject to reversible post-translational modifications, emerging as important epigenetic mediators of gene expression changes. Positively charged lysine residues cannot covalently bind to the negatively charged phosphate groups in the DNA but acetylation of a lysine residue removes the positive charge and reduces the histone-DNA interaction.[13]

Acetylation is mediated by histone acetylases (HAT) and results in activation of gene transcription while deacetylation by histone deacetylases (HDAC), prevents transcription. HATs are divided into group A, which are located in the nucleus, and group B, located in the cytoplasm. HDACs are divided into three classes. Class I HDACs are located in the nucleus and participate in transcription. Class II HDACs can be found in the nucleus and in the cytoplasm and mediate protein modifications, and Class III are associated with cell cycle.[10]

The structure indicates that highly basic histone amino (N)-terminal tails can protrude from their own nucleosome and make contact with adjacent nucleosomes. It seemed likely at the time that modification of these tails would

affect inter-nucleosomal interactions and thus affect the overall chromatin structure. Modifications not only regulate chromatin structure by merely being there, but they also recruit remodelling enzymes that utilize the energy derived from the hydrolysis of ATP to reposition nucleosomes. The recruitment of proteins and complexes with specific enzymatic activities is now an accepted dogma of how modifications mediate their function. Since chromatin is ubiquitous, modifications also affect many other DNA processes such as repair, replication and it includes post-translational modification of the N-terminal tails of histone proteins by acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, ADP ribosylation, biotinylation. Several families of enzymes catalyze post-translational modifications of histones, including acetyltransferases and deacetylases, methyltransferases and demethylases.[13] Multiple types of modifications can take place on a single histone molecule. The pattern of histone modifications determines chromatin status (euchromatin or heterochromatin), the accessibility of DNA to nuclear factors, and ultimately transcription. Alterations in chromatin structure due to histone modifications have been correlated with gene expression, the cell cycle, DNA replication and damage, DNA repair, and chromosome stability.

Histone acetylation results in a switch from repressive heterochromatin to permissive euchromatin. Increase in histone acetylation generally correlates with gene activation, and results from the dynamic interplay between histone acetyltransferases (HATs) and histone deacetylases (HDACs). Acetylation of histone tails is mediated by histone acetyltransferases (HATs) and results in an open modification of chromatin structure. It allows transcriptions factors to access the DNA and to initiate gene transcription. Conversely, gene repression is mediated via histone deacetylases (HDACs), which remove the acetyl groups from the histone tails, resulting in a closed chromatin structure.[4,14,15]

Histone phosphorylation Like histone acetylation, the phosphorylation of histones is highly dynamic. It takes place on serines, threonines and tyrosines, predominantly, but not exclusively, in the N-terminal histone tails. The levels of the modification are controlled by kinases and phosphatises that add and remove the modification, respectively[15]

Histone methylation, mediated by histone methyltransferases (HMTs), can have either positive or negative effects on gene expression. Histone methylation mainly occurs on the side chains of lysines and arginines. Unlike acetylation and phosphorylation, however, histone methylation does not alter the charge of the histone protein. Furthermore, there is an added level of complexity to bear in mind when considering this modification; lysines may be mono-, di- or tri-methylated, whereas arginines may be mono-, symmetrically or asymmetrically di-methylate.[4]

Histone modifications play an important role in chromosome structure, and silencing marks are enriched at silenced loci, such as imprinted genes, suggesting that they play a role there as well.

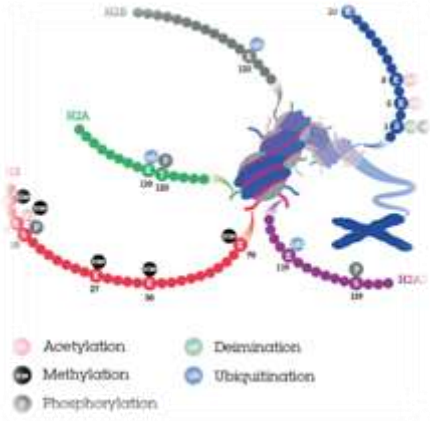


Figure 6:-

RNA Modifications

In 2006, Andrew Fire and Craig C. Mello shared the Nobel Prize in Physiology or Medicine for their work on RNA interference in the nematode worm C. elegans, which they published. RNA interference (RNAi) is a system involved in controlling gene activation in living cells. Two types of small RNA molecules – microRNA (miRNA) and small interfering /short interfering /silencing RNA (siRNA) – are considered as key mechanisms related to RNA interference. **Silencing RNAs**, represent a class of double-stranded RNA molecules, 20-25 nucleotides in length, that play a notable role in the RNA interference (RNAi) pathway,

where it interferes with the expression of a specific gene, but also in RNAi-related pathways as well as in antiviral mechanism or in shaping the chromatin structure of a genome. **Micro-RNAs (miRNAs),** are small non-coding RNAs, which play an essential role in modifying genes expression. The scientific community considers RNA interference the breakthrough biological discovery of the decade with the potential to change how diseases are treated.[16] RNA modifications have also been proposed to cause epigenetic changes.

ncRNAs such as transfer RNAs, ribosomal RNAs, microRNAs (miRNAs), and short-interfering RNAs (siRNAs) functionally resemble RNA molecules although they do not code for protein. miRNAs and siRNAs regulate gene expression without altering the DNA sequence. [17] 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. miRNA profiles can also be used to classify human cancers. Recently, much work has been carried out on the role of miR-21, miR-345 and miR-181b in oral cancer progression. 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.[17,18]

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.

Epigenetics in dentistry:

Epigenetics in development of oral cavity

Epigenetic factors present at each developmental stage can affect the developmental processes. Epigenetic mechanisms also play a crucial role in tooth development. Histone demethylase may regulate the dental stem cell differentiation. In addition, histone acetyltransferase and ncRNAs may influence odontogenic differentiation.[19] Fan et al. found that the oculofaciocardiodental syndrome, which is characterized by canine teeth with extremely long roots, is associated with a BCL-6 co-repressor mutation. This mutation leads to the upregulation of AP-2a in mesenchymal stem cells and promotes osteodentinogenesis.[17]

Dentinogenesis

Defects of dental enamel formation may be caused by genetic or environmental factors, including genetic polymorphisms and nutrient intake.[20] Expression of miRNAs is elevated during the last stages of osteoblast differentiation, demonstrating the importance of miRNA regulation for attenuating continued bone formation at the final osteocyte stage of differentiation. Dlx3 collaborates with transcription factors unique to mineralized tissue to regulate craniofacial and postnatal skeletal development. Dlx3 stimulates dentinogenesis. The posttranscriptional regulation of Dlx3 by miR-665 controlled by BMP2 and RUNX2, implies an combined network of signaling and transcription factors that coordinate the stage-specific events of odontoblast differentiation. KAT6A promotes RUNX2 acetylation to increase the transcription of genes involved in dentinogenesis. The multifunctional role of miR-665 highlights its function in controlling differentiation and tissue development. miRNAs link genetic and epigenetic events that are requisite for maintaining a normal tissue environment. The involvement of miR-665 at multiple levels of odontoblast differentiation suggests a therapeutic role for dental disorders.[17]

Epigenetics in oral pathology:

1. Leukoplakia
2. OSMF
3. Lichen planus
4. OSCC
5. BCC
6. Malignant melanoma
7. Sjogrens syndrome
8. Adenoid cystic carcinoma
9. Mucoepidermoid carcinoma
10. Odontogenic cysts
11. Odontogenic tumors
12. Autoimmuune disorders
13. Burkitts lymphoma
14. Oral inflammatory diseases

Potentially Malignant Disorders

Leukoplakia

Oral epithelial dysplasia, one of the common pre malignant white lesions of the oral cavity involves several epigenetic modifications. Hypermethylation of p14ARK, p16 INK4a, P15, MGMT, DAPK, GSTP1 and RARB have been seen in dysplasias and in histologically normal appearing margins of OSCC resections.[21] p16INK4a hypermethylation was significantly linked to LOH in two or more markers. These data support that INK4a/ARF locus alterations are frequent events preceding the development of oral cancer and that p16INK4a inactivation occurs to a greater extent in oral dysplasia than does p14ARF inactivation.[22] Validated target genes for miRNAs that function as TSG include Bcl-2, ras, myc, HMGA2, cyclin-dependent kinase 4 (CDK4), and CDK6, and target genes for miRNAs with oncogenic activity include PTEN, p27, p57, TIMP3, and BIM. miRNAs have been implicated in early disease. Cervigne et al found that miR-21, miR-181b, and miR-345 were consistently increased in oral dysplasia and associated with lesion severity.

Lichen Planus

Oral lichen planus (OLP) is a relatively common disease that affects the oral mucosa and is classified as potentially malignant disorder by the World Health Organization. 1% to 2% of OLP becomes malignant. the etiology of OLP is unknown, but consensus agrees that this disorder involves the immune system; thus, OLP is characterized as an autoimmune disease.

DNA methylation by hepatitis C, Epstein-Barr virus, human papilloma viruses, and H. pylori may be associated with the development lichen planus. Amalgam restoration is also related to the etiology of lichen planus because mercury may cause aberrant DNA methylation. Increased expression of DNMT may induce lichen planus via the hypermethylation of some genes by microbial infections. Decreased expression of E-cadherin and COX-2 indicates the risk of malignant transformation. Histone modifications occur in OLP, and H3K9ac and gH2AX histones may serve as epigenetic markers for OLP recurrence.[23,24]

OSMF

A chronic, progressive, disabling oral mucosal disease with a potential for malignant transformation is OSMF. It possesses a risk of 7.6% for malignant transformation over a period of 17 years. hypermethylation of p16 is an important factor to be considered in epigenetic alterations of normal cells to oral precancer, i.e. OSMF. E-cadherin and COX-2 expressions are related to OSMF. The epigenetic changes presented in patients with chronic inflammation might demonstrate an irreversible destruction in the tissues or organs similar to the effects of cancer. Chronic OSMF was significantly associated with hypermethylation, a cancer risk factor. [25,26,27]

OSCC

DNA Methylation

Hypermethylation and consequent silencing of several tumor suppressor genes, out of a group of more than 40 genes, has been identified in OSCC (Table); the genes found hypermethylated in OSCC cover a wide range of cellular processes, including cell cycle control (p16, p15), apoptosis (p14, DAPK, p73 and RASSF1A), Wnt signalling (APC, WIF1, RUNX3), cell-cell adhesion (E-cadherin), and DNA-repair (MGMT and hMLH1)[28] Methylation of CpG sites within promoter regions is an important mechanism for controlling gene expression in normal cells. Global analysis of CpG status in terms of methylation marks has proven to be useful for profiling the cancer epigenetic landscape. Therefore, it has been shown that approximately 5–10% of the CpG islands are aberrantly methylated within malignant pathologies, a fact that leads to the silencing of specific coding and non-coding genes (e.g., tumor suppressor genes) and implicit propagation of altered signals within specific pathways. However, despite the abnormal methylated status within cancer, the downstream effect does not consist of silencing the transcriptional and translational processes, a fact that suggests that the spatial context (localization of the CpG sites within the genome) is actually a crucial element in the establishment of gene silencing.[29]

Histone modifications:

Histones and chromatin modifiers mainly induce changes of chromatin architecture. Acetylation, methylation, phosphorylation and ubiquitination are major histone modifications, combination of which may constitute the "histone code" that extends and modulates the genetic code.[28]

The scientific insights describe that epigenetic alterations are observed at the N-terminal tails, within each of the four histone complexes (H3, H4, H2A, and H2B). Histone deacetylation catalyzed by various histone decetylases (HDACs) including HDAC1, HDAC2, and HDAC6 plays a significant role during oral carcinogenesis. There are

findings to support the overexpression of HDAC2 and HDAC6 in OSCC tissue and its association with advanced tumor stage, tumor size, and metastasis. One of the players in the histone epigenetic alterations is noted as HDAC2 and its expression is highly elevated in OSCC. Further, evidence leads to the idea that HDAC2 can be crucial for migration/invasion potential of OSCC. The authors extend the evidence to support that HDAC2 maintains hypoxia-inducing factor-1a (HIF-1a) stability and can lead to the enhanced cell invasion/migration ability in OSCC. Methylation of H3K4, H3K36, and H3K79 may play a role in activating histone marks that engaged in gene transcription activation. Furthermore, findings support that epigenetic alterations as HDAC carried out by various HDACs are crucial during oral carcinogenesis OSCC and possibly by stabilizing the HIF-1a.[29]
Among molecules that regulate the chromatin assembly, histone chaperones play an essential role. They drive histones incorporation into newly synthesized or remodelled chromatin. In this process, the Chromatin Assembly Factor-1 (CAF-1) exerts a pivotal role: it destabilizes heterochromatic structures during replication, allowing the replication machinery to progress through heterochromatin.[28]

MicroRNAs
MicroRNAs (miRNAs) are involved in many fundamental cellular processes such as proliferation, development, differentiation and apoptosis in normal and neoplastic cells, where they are referred to as oncomiRs (oncogenic miRNA). They act as mediators of epigenetic gene regulation, by interacting with mRNA, either by inhibiting mRNA translation or causing mRNA degradation.[28] It is important to note that plethora of miRNAs is reported to become notorious in the sense of acting as oncomiRNAs in OSCC and other carcinoma types. It has been suggested that epigenetic modifications and miRNAs are interlinked with each other in the expression pattern of genes such as Ras, p53, and B-cell lymphoma.[30]

Recent studies have been shown that miRNAs act as putative tumor suppressors and may also undergo epigenetic silencing in cancer. Although there are still few studies focusing on the miRNA involvement in oral carcinogenesis, the interest about their functional roles in OSCC is rapidly growing. The overexpression of miR21, miR181b, and miR345 may play an important role in malignant transformation. Wong TS found that the level of miR-133a and miR-133B was significantly decreased in OSCC when compared with normal epithelia samples. These low levels led to the activation of a potential oncogene pyruvate kinase type M2. Kozaki et al. investigated the miR-137 and miR-193a expression levels alteration in some OSCC cell lines, demonstrating that the epigenetic silencing of both miRNA, caused by DNA hypermethylation, could have a key function in oral cancer progression. Hu et al. demonstrated that miR-504 plays an important role during carcinogenesis, acting as a negative regulator of p53. In fact overexpression of miR-504 causes low demonstrated that miR-504 plays an important role during levels of the tumor suppressor. The potential role of miR-504 as new diagnostic, prognostic and therapeutic tools has been recently discussed by Wu et al. and by Gorennchtein et al., both hypothesizing a clinic advantage in OSCC patient management.[28]

Basal Cell Carcinoma
Basal Cell Carcinoma (BCC) accounting for approximately 70 % of all skin malignancies poses a significant public health problem despite its low mortality rate, since its incidence is continuously rising.[31] In addition to genetic changes, most cancers are characterized by epigenetic alterations capable of inducing tumour progression. Promoter hypermethylation of genes involved in fundamental cellular functions such as signal. transduction, apoptosis, adhesion, cell cycle, cytokine signaling, DNA repair, etc. has been reported to be an important epigenetic mechanism leading to gene silencing and consequently to tumourigenesis. Because of the inherent reversibility of epigenetic events, numerous targeted drugs are currently in the pipeline.[32] Along these lines, cutaneous malignancies represent an exciting field for the clinical application of epigenetic therapies. Relatively high frequency of RASSF1A, DCR1, DCR2 and APC promoter methylation may imply that methylation constitutes an important pathway in the tumourigenesis of BCC that could provide new opportunities in developing epigenetic therapies for BCC patients.[33]

Malignant Melanoma
Melanoma is a cutaneous neoplastic growth of melanocytes with great potential to invade and metastasize, especially when not treated early and effectively. Epithelial mesenchymal transition (EMT) is the process by which melanocytes lose their epithelial characteristics and acquire mesenchymal phenotypes. Mesenchymal protein expression increases the motility, invasiveness, and metastatic potential of melanoma. Many pathways play a role in promotion of mesenchymal protein expression including RAS/RAF/ MEK/ERK, PI3K/AKT/mTOR, Wnt/b-catenin, and several others.[34] Hypermethylation of specific tumor suppressor genes, as well as those involved in cell-cycle

regulation, DNA repair, cell signaling, transcription, and apoptosis, have been reproducibly described in cutaneous melanoma. The CDKN2A promoter has been shown to be hypermethylated in a substantial fraction of primary cutaneous melanoma samples and is associated with both increased Ki-67 index and reduced patient survival.[35] Of interest, CDKN2A, which encodes negative regulators of cell cycle progression p16 and p14 and is inactivated in the majority of sporadic cutaneous melanomas, is also the most frequently mutated gene inherited in familial cutaneous melanoma. RAS association domain family protein 1A (RASSF1A), which is critical for mitochondrial apoptosis and cell cycle arrest, was found to be methylated in 57% of melanoma specimens, O6-methylguanine DNA methyltransferase (MGMT, discussed in greater detail below) in 34%, and apoptosis mediator death-associated protein kinase in 19%.[36] Indeed, the number of tumor suppressor genes that are hypermethylated in melanoma is accumulating. By contrast, specifically hypomethylated genes have been less documented in melanoma. Histone hypoacetylation has been demonstrated to downregulate other proapoptotic proteins, including the Bcl-2 family proapoptotic proteins (Bim, Bax, and Bak), as well as tumor suppressor genes, such as phosphatidylinositol 4, 5-bisphosphate 5-phosphatase A, a negatively regulator of the PI3K/Akt signaling pathway. miR-200c was shown to be significantly more downregulated in both primary and metastatic melanomas compared with benign melanocytic nevi, and its overexpression in melanoma cell lines appears to result in significantly reduced cell proliferation, migratory capacity, and expression of key transporters involved in melanoma drug resistance.[37]

More importantly, the loss of E-cadherin as well as the aberrant expression of neural cadherin (N-cadherin) marks the critical transition from the radial-growth phase to the vertical-growth phase in melanoma, an event that is associated with acquisition of potential for metastasis, has also been reported. The expression of aVb3 integrin, which, in addition to E-cadherin loss and N-cadherin expression, also tightly associates with the transition from the radial- to vertical-growth phase in melanoma.[34]

Salivary Gland Lesions

Sjogrens syndrome

In Sjogren's syndrome (SS), a chronic autoimmune disorder, characterized by exocrine gland dysfunctions and lymphocytic infiltrations. The epigenetic studies have focused on three mechanisms: DNA methylation and its consequences including human endogenous retrovirus (HERV) expression; microRNA expression; and protein post-translational modifications associated with autoantibody production. Although in its infancy, comprehension of the epigenetic (dys)regulation in SS may help us to understand: why SS affects predominantly middle-aged women; why genetically predisposed individuals develop SS but not others; why flare-ups occur; why treatment responses differ between patients; and why some patients develop lymphoma. From these studies will arise a better comprehension of the pathophysiology of SS as well as development of new diagnostic and prognostic biomarkers, and novel therapeutics for prevention and perhaps early intervention[38,39]

MEC

Mucoepidermoid carcinoma (MEC) is the most common type of salivary gland malignancy in adults and children. MECs arise more commonly in the parotid than the minor salivary glands, wherein the soft and hard palate are the main sites of involvement. To date, only a few methylation studies have focused on MEC carcinogenesis. Protein levels of E-cadherin and secreted frizzled-related proteins. (SFRPs) were down-regulated due to their promoter hypermethylation. Promoter hypermethylation was also found in some tumor suppressor genes (TSGs), including p16INK4a, runt-related transcription factor 3 (RUNX3), O6 -methylguanine-DNA methyltransferase (MGMT), retinoic acid receptor b2 (RARb2), RAS-associated domain family protein 1A (RASSF1), adenomatous polyposis coli (APC), and death-associated protein kinase (DAPK). However, there has not been a genome wide study looking at the profile of CpG methylation in the DNA promoter regions in MEC.[40] Hypermethylation of p14 appears to be an important event in the development of 65 mucoepidermoid carcinoma. High frequency of gene hypermethylation and high incidence of methylation at multiple sites point to the importance of epigenetic phenomena in the 67 pathogenesis of MECs, although with modest impact on clinical parameters.[41]

AdCCa

Adenoid cystic carcinoma (ACC), a relatively rare malignancy usually of salivary gland origin, has a signature v-myb avian myeloblastosis viral oncogene homolog–nuclear factor I/B (MYB-NFIB) gene fusion that activates MYB transcriptional regulatory activity. mutations in SPEN (split ends, homolog of Drosophila), which encodes an RNA-binding coregulatory protein, suggest that other changes in transcriptional regulation may involve the NOTCH, FGFR, or other signaling pathways in which SPEN participates. Since there is a low prevalence of mutations in common oncogenes and tumor-suppressor genes, it is likely that alterations primarily in specific transcriptional

regulatory genes, augmented by changes in chromatin structure, drive the neoplastic process in ACC.[42] Interestingly, mutations selectively involved chromatin state regulators, such as SMARCA2, CREBBP, and KDM6A, suggesting aberrant epigenetic regulation in ACC oncogenesis. Mutations in genes central to DNA damage and protein kinase A signaling also implicate these processes. MYB-NFIB translocations and somatic mutations in MYB associated genes, solidifying these aberrations as critical events was also observed with recurrent mutations in the FGF/IGF/PI3K pathway that may potentially offer new avenues for therapy (30%).[43]

Odontogenic Cysts

Radicular cyst

The methylation pattern of the promoter region CpG from the IFNG gene presented partial or total methylation of the promoter region of the gene, which suggests that this epigenetic alteration is a common alteration in periapical inflammatory lesions. In addition, an increased methylation profile in radicular cysts is found when compared with periapical granulomas. methylation of the IFNG gene is a frequent event in periapical lesions and methylation of the gene is associated with distinct mRNA transcription levels of the gene. [44,45]

OKC

The PTCH1 methylation has been suggested as an alternative to mutational causes of the PTCH pathway deregulation in tumours associated with NBCCS syndrome, such as meduloblastoma and basocellular carcinoma. In contrast to dental follicles, OKC samples presented methylation of the P21 gene. Epigenetic alteration of the RB1 gene was detected in some samples of dental follicles but in none of the OKC samples.[46,47]

Odontogenic Tumors

Expression of MMP-9 is increased in ameloblastomas and is possibly modulated by unmethylation of the gene**.** [47,48]

Autoimmune Disorders

SLE

SLE is a type of systemic autoimmune diseases, which involves a complicated interaction between the innate and the adaptive immune system loss of immunological tolerance to self-nuclear antigen, and antibody production. Notably, DNA hypomethylation and reactivation of the inactive X chromosome are two epigenetic hallmarks of SLE. CD11a, perforin and the KIR genes were overexpressed in patients with active, but not inactive, lupus, and the same sequences demethylated in proportion to disease activity and gene overexpression in these patients. In CD4+ T cells of SLE patents, it has been identified that global histone H3 and H4 are hypoacetylated and global histone H3K9 is hypomethylated. The X chromosome of SLE women is demethylated, which may be the reason of the predominance of SLE in women. There are altered expression levels of certain lncRNAs in SLE. Profiling of the miRNAs expressed in the peripheral blood mononucleated cells (PBMCs) from lupus patients revealed that miR-146a was underexpressed in SLE. A further study found that STAT1 was another target of miR-146a, and there was a reverse correlation of miR-146a levels with the expression of interferon-inducible genes and SLE disease activity.[49,50]

Pemphigus Vulgaris

PV is a prototypical organ-specific human autoimmune disease caused by autoantibodies to keratinocyte cell adhesion proteins known as Dsgs. Several studies have indicated that environmental factors contribute to the pathogenesis of pemphigus, such as virus infection, and exposure to pesticides, metal vapour and sunlight. Epstein–Barr virus, which was implicated as a cause of pemphigus, increases DNA methylation of E-cadherin gene and p16INK4A and represses BIM (BCL2L11) gene transcription initially involving the epigenetic modification H3K27 trimethylation during lymphomagenesis. A distinct DNA hypermethylation pattern in epidermal skin can be induced by exposure to ultraviolet B radiation, and sun exposure has been reported to exacerbate PV. Moreover, pesticides, air pollutants, industrial chemicals and heavy metals have also been reported to change gene expression through histone modifications and DNA methylation. These studies suggested that epigenetic modifications may be involved in the development of PV. Epigenetic modifier genes such as DNMT1, MBD3 and HDAC1 with altered mRNA expression may contribute to aberrant epigenetic patterns in PBMCs of patients with pemphigus vulgaris.[51,52]

Burkitts Lymphoma

All Burkitt lymphomas (BLs) carry reciprocal chromosomal translocations that activate the c-myc oncogene through juxtaposition to one of the immunoglobulin (Ig) loci. Many BL carry point mutation in the p53 tumor suppressor gene or other defects in the p14ARF–MDM2–p53 pathway, and inactivation of the p16INK4a gene by promoter

methylation or homozygous deletion. This indicates that disruption of both the pRb and p53 tumor suppressor pathways is critical for BL development. Alterations of other genes, including Bax, p73, and BCL-6, may provide further growth stimulation and apoptosis protection. Thus, BL development involves multiple genetic and epigenetic changes that drive cell cycle progression and avert cell death by apoptosis.[53]
HACE1 can be downregulated by methylation of its promoter region chromatin (H3K27me3 and H3K9me2), making HACE1 a potential target for DZNep combined with TSA. These results highlight the heterogeneity of HACE1 regulation in B-lymphoma and suggest that successful drug-induced restoration of epigenetically silenced tumor suppressor genes will require accurate characterization of cell type- and locus specific gene silencing mechanisms.[54]

Oral Inflammatory Diseases

Little is known about the epigenetics of oral inflammatory diseases, although epigenetic mechanisms in systemic inflammatory diseases, such as autoimmune diseases, are well documented. Recently, epigenetic modifications have been observed in chronic periodontitis. Hypermethylation of TLR2, TNFα, E-cadherin and COX-2, and hypomethylation of IFN-γ were detected in chronic periodontitis. In patients with chronic periodontitis, decreased expression of TNFα and COX-2, and increased expression of IFN-γ were confirmed. It is not known whether these aberrant methylations are specific to chronic periodontitis. Recently, genome-wide analysis using a CpG island microarray elucidated the methylation profile of periodontal disease. The gingival sulcus epithelium in periodontal disease revealed hypermethylation of cytokine-producing genes, including TYK2, IL17C, IL12B, CCL25, CXCL14, IL4R, IL13, GATA3, IL13RA1, IL6R, and CXCL5.[55]

Conclusion:-

The era of epigenetics is upon us, and in the words of James D. Watson; 'What determines whether a given piece of DNA along the chromosome is functioning, since it's covered with the histones? You can inherit something beyond the DNA sequence. That's where the real excitement of genetics is now.' Unlike genetic alterations, epigenetic changes are potentially reversible, and this feature makes them attractive targets for therapeutic intervention. As the role of epigenetics in oral lesions becomes clearer and the interrelationships between chromatin components are increasingly understood, we are at a good point to re-evaluate our approaches to disease prevention, detection, and therapy. Epigenetic changes offer new therapeutic targets, which have yet to be explored in oral squamous cell carcinoma, but have shown promise in other tumour sites.

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