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## RESEARCH ARTICLE

### EPIGENETIC MODIFICATION OF GENES INVOLVED IN LATENCY OF VIRUSES CAUSING ORAL DISEASES.

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#### Abstract

Viruses encompassing the members of the herpes simplex viruses (HSV), human immunodeficiency viruses (HIV), respiratory viruses inclusive of adeno, respiratory syncytial viruses and influenza viruses, oncogenic viruses like polyoma and papilloma are presently the subject of intense interest with respect to epigenetics playing its role in implementing various oral health issues. In near decades, primary focus may be oriented towards the role of histone modification, nucleosome location and DNA methylation in regulating the biological consequences of oral viral infections. These epigenetic mechanisms underlying oral viral illnesses are understood by a wide variety of strategies and techniques used to identify the histone modifications and DNA methylation site. Aim of this review is to highlight the epigenetic mechanisms behind oral viral diseases which may play an inherent role in the regulation of the viral genes and their transformation in the oro-mucosal layers.

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#### Introduction:-

Epigenetics involves alteration in the pattern of gene expression without any change in the DNA sequence. These “tags” are heritable and has a transgenerational effect. Chemical modifications of DNA such as DNA methylation, histone modifications, micro-RNAs and nucleosome positioning, either selectively activate or inactivate genes, thereby manipulating the expression. Studies on the epigenetic mechanisms in pathogen induced cancer types have instigated research on pathogen mediated epigenetic reprogramming of host cells [Flanagan et al., 2007]. In this context, knowledge about the epigenetic mechanisms in the course of viral infection is worth exploration, as co-evolution of virus with their host has provided unique ability to evade and exploit the host system for their proliferation. Persistent viruses that cause latent infections benefit from these processes as the host environment is modified so as to sustain them in a latent state. This eventually reduces their burden of initiating the process of revival from time to time. They are also found to conquer the host transcription machineries and epigenetic regulators, thus controlling the host gene expression by silencing host genes encoded in the chromosomal clusters (Adhya et al., 2010). Genes controlling the survival, senescence, cell cycle, inflammation and immunity are the primary targets of such modification processes (Virgin et al., 2009). Although the latency is not influenced by DNA methylation, chromatin remodelling seems to be a vital process during this term of infection (Deshmane et al., 1989). Designing anti-viral agent has become a herculean task due to increasing mutations which has led to more virulent form of viruses. In such situations, the focus of researchers have moved towards developing specific inhibitors for those effector proteins involved in epigenetic silencing of host immune system. However, the infection combating mechanisms of the host can never be misjudged. Nucleosome remodelers have been identified which causes repression of viral infection during the early stages (Arbuckle et al., 2014). The aim of this review is to unravel the processes adopted by the viruses to overcome the host immunity for their sustenance and latency.

#### Epigenetic mechanisms underlying oral warts:-

Recurrent herpes labialis or oral warts caused by Herpes simplex virus Type 1 (HSV-1) is the most ubiquitous communicable infectious viral disease in the oral cavity. HSV-1 infection afflicts to approximately one third of the

world's population with one half of them suffering multiple attacks annually (Elad et al., 2010). HSV infections are either productive or non-productive and results in acute, latent or recurrent infection and sometimes oncogenic. HSV-1 remains latent between episodes of disease in the trigeminal ganglia and these latent viruses in the ganglionic cells exist as non-replicating latent entities (Looker et al., 2005). Although the detailed aspects of recurrent HSV infection are relatively unknown the ganglionic latent HSV serves as the source of virus in the recurrent warts disease in the oral cavity.

HSV-1 undergoes a lytic infection in the oral epithelial cells and experiencing a latent infection in the neuronal cells, the epigenetics in the differential HSV gene expression occur under two conditions. HSV virions are not associated with histones but are rapidly loaded with heterochromatin upon entry into the cell. The viral proteins promote reversal of the epigenetic silencing in oral epithelial cells while the viral latency associated transcript promotes additional heterochromatin in neuronal cells (Knipe et al., 2015). However, initiation of the chromatinization of foreign DNA by the cellular sensors has not been fully defined. New evidence shows that IFI16 (Interferon  $\gamma$ -inducible protein 16) and cGAS (cyclic guanosine monophosphate-adenosine monophosphate synthase) are essential for innate sensing of HSV DNA to initiate signalling. IFI16 plays a role in the hetero-chromatinization of HSV DNA that integrates epigenetic regulation and innate sensing of foreign viral DNA in the initiation of oral illness (Johnson et al., 2013).

#### **LAT mediated repression of HSV-1:-**

The latency associated transcript (LAT) is abundantly transcribed during the period of latency (Feldman et al., 2002). LAT is a non-coding polyadenylated RNA of approximately 8.3-8.5 Kb in length (Hill et al., 1990). The transcript produced has a long half-life and exerts pleiotrophic effect on the phenotype such as establishment of latency (Thompson et al., 2001), reactivation (Leib et al., 1989), and blocking of apoptosis (Perng et al., 2000). Post translational modifications of histone proteins have been demonstrated in the euchromatin or heterochromatin of the HSV-1 genes during latency, which indicates that the control of gene expression is present at the chromatin level. Acetylation of histone H3 and dimethylation of histone H3 are modifications observed in the areas of euchromatin at the LAT locus which is indicative of the fact that virus mimics the histone modifications similar to that of host cells (Neumann et al., 2007).

#### **Polycomb and CTCF proteins mediated repression of HSV-1:-**

The association of HSV viral genome with the PRC2 (polycomb repressor complex) is yet another mechanism by which the repression is enabled. The EZH2 portion of the PRC2 complex is known to catalyze the trimethylation of H3 K27, thus creating repressive marks on the genome. In order to preserve these marks PRC1 is recruited to the site which then replaces PRC2 proteins, thus establishing latency. External stress stimulus induces reactivation by displacement of PRC1 complex and demethylation of H3 K27 (Kwiatkowski et al., 2009). CTCF (CCCTC binding protein) has been reported to block the LAT enhancer from activating the lytic gene promoters. This process ensures transcriptional repression of gene involved in the lytic pathway. Hence, premature reactivation of the lytic cascade is averted (Amelio et al., 2006). Although studies on the epigenetic control of HSV-1 latency are still in the juvenile state, the mechanisms studied so far gives a clear outline of the reversible repression mechanism involved in lytic pathway.

#### **Epigenetics repression of cytomegalovirus in the oral cavity:-**

Cytomegalovirus is yet another antigenically distinct member of herpes viruses and has a narrow host range and nearly species specific. Replication is slow and inefficient and causes latent infection in salivary glands, epithelial cells and certain leukocytes (Manning et al., 1992). The latent CMV can be reactivated during periods of reactivation in the oral epithelial cells. Tropism of the salivary gland is central to the biology and epidemiology of CMV's (Lagenaur et al., 1994). In addition to the studies on human CMV, studies associated with the murine CMV also provides a useful setting to assess the viral genes that are dispensable for growth in cultured cells influencing tissue tropism, pathogenesis or latency and also temperature sensitivity (Sammons et al., 1989). The associated genetic mechanisms reduce the CMV ability to grow in salivary glands, but however, the mutations responsible for this behaviour are yet unclear.

Targeted DNA methylation has been demonstrated in genome integrated CMV and adenovirus type E1A promoters. These promoters are hypermethylated after MCF7 and HEC K293 cells are transfected with in vitro methylated viral promoter fragments. These targeted methylation induced gene silencing can often be reversed by addition of 5-aza-2'-deoxycytidine and further confirms that CMV and E1A promoters are regulated by DNA methylation (Hsu et al.,

2010). In the live cells, the kinetics of DNA methylations determines the reporter system. In CMV this pattern of targeted DNA methylation is able to efficiently silence susceptible viral promoters thus providing an alternative strategy to study the impact of loci – specific DNA methylation in the CMV viral genome expression establishing oral illnesses.

#### **Epigenetic modulations in HIV and associated oral illness:-**

HIV associated oral illnesses occur in a large proportion of patients and are frequently misdiagnosed or inadequately treated. Common or notable HIV-related oral conditions include xerostomia, candidiasis, oral hairy leukoplakia, periodontal diseases such as linear gingival erythema and necrotizing ulcerative periodontitis, Kaposi's sarcoma, human papilloma virus-associated warts, and ulcerative conditions including herpes simplex virus lesions, recurrent aphthous ulcers, and neutropenic ulcers (Reznik, 2006). Also HIV related oral abnormalities are present in 30% - 80% of HIV infected individuals and only 9.1% patients receive appropriate treatment (Dios et al., 2000).

#### **Methylation and histone modification mediated suppression of HIV:-**

Methylation of viral genes and histone modifications contribute to initiate and maintain HIV latency (Verma et al., 2015). It is now understood that the epigenetic mechanisms in HIV not only play a crucial role in gene expression but also in the pathogenesis of HIV with a broad range of oral illnesses. Epigenetic regulation is being determined by the establishment and maintenance of HIV-1 latency and in the reactivation of HIV-1 by periodontopathic bacteria (Jordan, 2013). Effect of histone modification on transcriptional regulation is being focused in HIV-1 gene expression during lytic and latent stages of HIV-1 infection (Imai et al., 2011).

Methylation of histone protein leads to repression of genes present in the heterochromatic regions. This repression may be facultative (temporary) or constitutive (permanent). The temporarily silenced gene may be identified by H3K27me3 mark (Trojer et al., 2007). Addition of di and tri-methyl groups to H3K27me3 is catalysed by polycomb repression complex present in the mammalian cells (Margueron et al., 2007). An enzymatic component of the PRC complex, called EZH2 (Enhancer of Zeste protein) is known to initiate this process, which is crucial for the establishment and sustenance of HIV-1 silencing. Knockdown studies have proved that EZH2 are potent inducers of facultative heterochromatin which leads to activation of latent HIV-1 by exogenous signals (Kuzmichev et al., 2002).

Histone methyltransferases are known to modify histone proteins. Gene silencing may be induced by the recruitment of SUV39H1 and G9a which are involved in heterochromatin formation at the HIV promoter (Du Chene et al., 2007). Histone deacetylases (HDACs) are crucial components which act in response to Ying Yan 1 (YY1) and late SV-40 (LSF) transcription factors and repress HIV transcription and viral production (Van Lint et al., 1996).

#### **Epigenetic repression of EBV:-**

Epstein Bar virus was suggested as the causative agent of infectious mononucleosis and is antigenically unrelated with the other herpes viruses. EBV infects the B cells *in vitro* and can also establish a latent infection in B cells. EBV also persists in peripheral blood lymphocytes for years after infection. EBV is known to infect the epithelial cells of the tongue in patients with AIDS or AIDS related complex (ARC) or the nasopharynx. Infected cells may undergo blast transformation and go into long term culture (immortalization) (Halder et al., 2009). EBV also presents a white corrugated lesion on the lateral borders of the tongue (Walling et al., 2003).

#### **miRNA mediated repression of EBV:-**

Epigenetics behind EBV studies portrays the role of microRNA's having a negative effect on the gene expression and is considered to be the major players in cell function in normal and pathological conditions. EBV infection of resting B lymphocytes results in their growth transformation and is highly associated with different B cell lymphomas. Major changes in gene expression is involved in EBV mediated B cell transformation including cellular miRNA's. Expression of miRNA analysis in growth transformation of EBV infected B cells is being studied (Vento-Tormo et al., 2014). Similar observations are profiled with the miRNA expression in B cell stimulated with CD40L/IL-4 and those infected with EBNA-2 (Epstein Barr virus nuclear antigen) and LMP-1 (Latent Membrane Protein 1) deficient EBV particles, suggesting the implication of NFκB pathway. In fact NFκB subunit p65 associates with the transcription start site (TSS) of both upregulated and downregulated miRNA following EBV infection. Epigenetic mechanism underlying this gene regulation involves changes with histone H3K27me3 and histone H3K4me3 expression (Murata et al., 2012). Inhibition of NFκB pathway impairs changes in miRNA expression, NFκB binding and changes related to histone modifications near the TSS of the miRNA genes. These

mechanisms highlight the epigenetically mediated NF $\kappa$ B pathway and miRNA controlled B cell transformation in EBV oral infections.

#### **Epigenetic mechanisms in oncogenic viruses behind oral and craniofacial layers:-**

Oncogenic viruses like papilloma and papova viruses can produce productive and non-productive illnesses of the cutaneous or mucosal epithelial layers inclusive of the oral cavity resulting in warts, and other self-contained benign lesions that commonly regress. Productive viruses lead to the production of progeny viruses and the non-productive infection lead to the abortive transformation of the cells. Human papilloma viruses (HPV's) and a subset called mucosotropic HPV's is etiologically associated with numerous cancers of the craniofacial layers. In these cancers, HPV genome normally exists as a double stranded, circular, nuclear plasmid and is commonly found to be integrated into the host genome and expresses two viral oncogenes E6 and E7, that are implicated in the development and maintenance of the cancers caused by these high risk HPV's. Documentation of the HPV 16 methylation status of the viral genome changes is dealt in terms of progressive neoplastic disease that culminates in cancer. Chip-seq data analysis suggests the occupancy of both epigenetically modified histones as well as transcription factors on the high risk HPV 18 genome (Eric Johannsen et al., 2013).

The unregulated expression of critical viral genes redirects the cellular gene expression. The redirected cellular expression is thus a consequence of either epigenetic regulation where cellular signalling or transcriptional dysregulation occurs or direct epigenetic regulation where epigenetic cofactors like histone deacetylases are targeted. Epigenetic modulations in AIDS defining malignancies like Kaposi's sarcoma and non-Hodgkin lymphoma also influences the variations in the oral infections (Balderas-Loaeza et al., 2007). Oncogenesis in conjunction with HIV can cause epigenetic changes at the viral promoter and can result in altered gene expression, and exacerbate disease progression overall, especially in the oro-mucosal areas (Chiappelli et al., 2008). The impact of this interplay on disease progression at the level of chromatin accessibility, chromatin remodelling and nucleosome repositioning is reported with the oncogenic transformation of the epithelial layers. Importance of chromatin remodelling and DNA methylation in controlling the viral promoter favours the control of oral health illnesses (Shirazi et al., 2013).

#### **Conclusion:-**

To date, molecular viral epigenetics examines non-coding DNA versus coding DNA and is pertained to every domain of viral physiology, immuno-pathogenesis and other associated health illness like oral diseases. Molecular cartography, including genomics, proteomics and interactomics, identifies the multi-faceted viral replication and intricate array of interacting genes and gene products that characterize the gene function (Milavetz et al., 2015). This specialize each individual viral cell in the context of cell-cell interaction, tissue or organ function. Thus an understanding of viral epigenetics and chromatin assembly, repair and remodelling together with the RNA interfering signalling complex is necessary. Primary focus on the role of histone modification, nucleosome location and DNA methylation regulates the biological consequences of viral replication and directly associates with the oral ill health. Wide variety of studies portrays that epigenetic regulation of viruses and oral diseases are slow without clarity. While the viruses differ in significant ways from each other and cellular chromatin, the role of epigenetics appear to be relatively similar. Within the viral genome, nucleosomes are organized for the expression of appropriate genes with relevant histone acetylation. This pattern of unregulated gene expression of critical viral genes is capable of redirecting the cellular gene expression and exerts a mild and moderate effect on oral diseases. Indirect epigenetic modulations like cellular signalling or transcription dysregulation and direct epigenetic regulation like histone deacetylation targets the viral life cycle and varying patterns of oral diseases. Nevertheless, yet unclear factors are still in line to be explored in the context of underlying viral epigenetics in oral diseases.

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