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REVIEW ARTICLE

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The influence of epigenetics in relation to oral health

Abstract: The immune response is influenced by genetic and epigenetic factors, as well as disease and environmental factors. The term 'epigenetics' describes changes in the genome that influence the gene expression without altering the DNA sequence. In contrast to genetic changes in the DNA, epigenetic changes are reversible and are influenced by environmental factors. The aim of this study is to review the literature on epigenetic modifications with respect to oral health and inflammatory conditions in the oral cavity and to discuss the potential use of this new research field for the dental hygienists' and/or dentists' clinical work. Relevant publications were identified using the PubMed database without limits. The searches were conducted during January to March 2012 and resulted in articles published between 1912 and 2012. Key factors such as environment, diet, smoking, bacteria and inflammation were identified to be relevant to oral health. The result of this review article shows that there is a void in the research on epigenetics in relation to oral health. Identification of epigenetic modifications correlating with oral health may not only present a link between the influence of genetics and that of the environment on oral diseases but also provide new treatment models and tools for the dental professionals.

Key words: diet; epigenetic; inflammation; oral health; smoking

Introduction

The immune response is not only regulated by genetic factors, but there is a second level of regulation related to the chromatin status of the DNA. The term 'epigenetics' describes changes in the genome that influence the gene expression without altering the DNA sequence (1). Epigenetic modifications include chemical alterations in the DNA and its associated proteins. These alterations lead to remodelling of the chromatin resulting in activation or inactivation of a gene, thus contributing to the development of cancer, autoimmune diseases as well as inflammatory diseases (2, 3). The term 'epigenome' has been proposed as a term describing the chromatin and its related proteins and modifications (Fig. 1) and presents a link between the inherited genome and the environment (4). In contrast to the DNA sequence, the epigenetic process is dynamic and changes during life in response to diseases and environmental factors, such as diet, smoking and age (3). The growing knowledge about epigenetics contributes to a better understanding regarding the interactions between genes and the environment and may provide explanations to why patients with the same clinical phenotype respond differently to treatment (5).

The major epigenetic modifications are DNA methylation and histone acetylation and methylation (6) (Fig. 2). DNA is stored in the cell

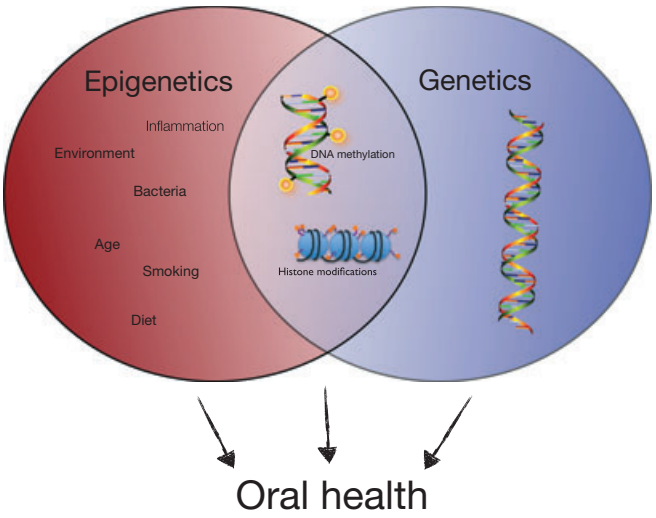

Fig. 1. Schematic drawing of the interaction between the environment and genetics.

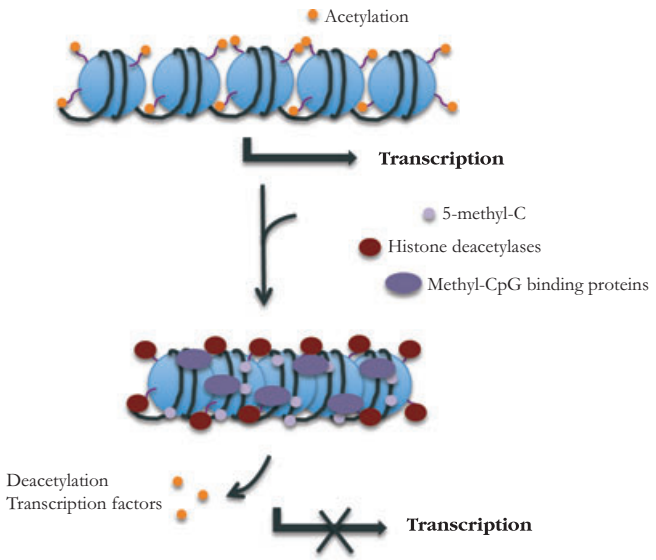

Fig. 2. Mechanism for gene silencing by DNA methylation and histone deacetylation. A transcriptional active gene is characterized by histone acetylation and an open chromatin structure. Deacetylation of the gene forms a tightly packed structure that inhibits gene expression.

nucleus as a chromatin complex, consisting of DNA wrapped around histones. The histones may be acetylated and/or methylated, and the resulting combination of histone modifications promotes unique cellular responses by changing the ability of the transcription factors to bind to DNA and hence initiate gene expression (7, 8). Histone acetylation is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone deacetylases remove acetyl groups, which leads to alteration in the packing of DNA around histones (9). A more compact chromatin is associated with transcriptional inactivation, and a more loosely packed chromatin is associated with transcriptional activation (8, 10). The DNA itself can be modified by the addition of methyl groups to specific DNA sequences with cytosine and guanine bases separated by a phosphate molecule, so-called CpG islands. This process is regulated by DNA (cytosine-5) methyltransferases (DNMTs). Aberrant DNA methylation is associated with tumorigenesis as well as inflammation (9, 11, 12).

Epigenetic modifications of a certain part of a gene can differ between cell types and may result in a different local and systemic expression of a gene. Research on epigenetic modifications in combination with genetic analysis may provide further evidence to interindividual differences in local expression of genes associated with inflammation. Chronic inflammatory diseases, such as periodontitis, have specific target tissues in which inflammation is persistent and tissue destruction occurs. Gingivitis is a periodontal disease characterized by inflammation in the gingival connective tissue. Periodontitis is characterized by chronic inflammation in the gingival tissues, but with associated loss of connective tissue attachment and loss of supportive bone. Periodontitis is a common disorder, and severe forms of the disease occur in about 10% of an adult population (13). Periodontitis has been characterized by Kornman (14) as a result of bacteria colonizing the tooth surface and the host response, which in turn is influenced by both genetic and epigenetic components. In 1976, Loevy presented a review of the genetic aspects of the pathogenesis of periodontitis (15). Even though research on periodontitis over time has contributed to a more comprehensive knowledge of the disease, there are still many pieces missing (14).

Objective

The focus of this article is to review the literature in the field of epigenetics in relation to oral health and in particular in relation to inflammatory diseases in the oral cavity, for example gingivitis and periodontitis.

Method

Literature search

The literature search was conducted using the database PubMed during the period January to March 2012. We started the search using the keywords 'epigenetic' and 'methylation' that resulted in 22 283 and 59 245 articles published between 1912 and 2012. The additional keywords 'periodontal disease' and 'periodontitis' were then used to broaden the search and resulted in a total of 69 248 and 24 742 articles, respectively. In the next step, based on the identified articles, key factors such as environment, diet, smoking, bacteria and inflammation were used to limit the search to 488 articles. Finally, 40 articles were identified to be relevant to oral health. The results are presented and discussed under the following sections as follows: Diet, smoking and environmental factors; Bacteria; Inflammation; Treatment; and Future research.

Results and theoretical reflection

Diet, smoking and environmental factors

Diet and smoking are factors known to influence the oral health. Different nutrition influences the presence of caries (16), and smoking is a well-known risk factor for periodontitis (17). However, the exact epigenetic mechanisms are not known, and therefore, further studies on the effect of these factors on the different tissues in the oral cavity will provide an increase in knowledge that could be of great interest for the dental hygienist working in preventive dentistry.

Investigating the influence of environmental factors on epigenetic mechanisms in humans is difficult because it has to be established that changes seen in gene expression are not caused by genetic factors. The use of the twin model has the advantage of homozygote twins having the same genome but different epigenome, indicating that differences in disease susceptibility are caused by factors other than genetics. Fraga *et al.* (18) demonstrated that 35% of the monozygotic twins in their study differed in both methylation and histone pattern. These differences also increased as the twins grow older, together and by differences in disease history. Furthermore, a comparison of epigenetic patterns in 3-year-old twins with those of 50-year-old twins showed large difference in gene expression patterns between the age groups. This is in line with the present view that epigenetic changes increase during life and that age itself is a 'risk factor' for epigenetic changes. In the study by Fraga *et al.* (18), it was suggested that the changes in epigenetic modifications between the monozygotic twins were caused by environmental factors such as smoking and diet. These findings are supported by the results presented by Seddon *et al.* (19) in a similar study on monozygotic twins with age-related macular degeneration (AMD), a disease associated with inflammation and that results in a partial loss of vision. The results showed that the twin who smoked the most had a higher degree of the AMD disease compared with the twin smoked less. In addition, Seddon *et al.* suggested that behaviour and nutrition factors, such as vitamin D, betaine and methionine, cause epigenetic changes and thereby influence disease progression. The epigenetic changes caused by a certain diet do not affect the individual at only the time of dietary intake. Animal research has demonstrated that not only does the mother's diet influence foetal development but it can also affect the offspring as an adult, and in particular in long-term diseases such as cancer (20–22).

Several nutrition factors, such as folate, vitamin B12 and vitamin A, may result in changes in epigenetic modifications. Folate is a water-soluble vitamin present in dark green leafy vegetables, strawberries and asparagus. It has been studied extensively in relation to cancer because of its ability to add methyl groups thereby changing DNA methylation. Thus, a decrease in folate intake causes a subsequent decrease in DNA methylation. DNA hypomethylation is a key feature of cancer affecting the expression of genes related to tumorigenesis. It has been suggested that DNA hypomethylation can be used not only as an indicator of lack of folate but perhaps also as one mechanism to alter the risk of cancer (23–25). In addition, Schernhammer *et al.* (25) showed that a low intake of folate as well as alcohol consumption might be risk factors for hypomethylated colon cancer. In squamous cell carcinoma of the head and neck, alcohol was also found to be associated with changes in the methylation pattern (26). Most of the studies investigating the effect of nutrition on the epigenome have focused on DNA methylation. However, histone modifications are closely regulated and reversible mechanisms, and sulphoraphane, a compound found in cruciferous vegetables, has been found to cause the inhibition of HDACs and this substance has been introduced as a cancer therapy (22, 27, 28). In addition, compounds from garlic and grapes alter both acetylation and deacetylation patterns, but at present, the effect of these compounds on gene expression and disease is not fully understood (29).

As discussed in the review by Su *et al.* (22), it is not only the nutrition compounds in the diet that affect epigenetic mechanisms. Through the diet, an individual may be exposed to toxicants present in the food or water, for example arsenic, cadmium, mercury and nickel. However, few studies have investigated the correlation between epigenetic mechanisms and environmental factors other than nutrition and smoking. The effects of arsenate in drinking water were investigated by Cui *et al.* (30). The authors found that arsenate exposure resulted in arsenic accumulation in the lungs and development of lung tumours. It also caused hypermethylation, thereby silencing tumour suppressor genes.

Smoking causes long-term hypo- and hypermethylation changes in the DNA. These changes are present not only in current smokers but also in former smokers (31, 32). Haffajee and Socransky (17) found that smokers had a more severe form of periodontitis with more attachment loss and deeper pockets compared with former smokers and non-smokers. The results of this study also indicated an association of increase in attachment loss with age as well as disease severity. An association between age and risk of periodontitis was also presented by Papapanou and Lindhe (33). The increase in attachment loss may be a result of epigenetic changes as Ohi *et al.* (34) showed an increase in methylation in the collagen type 1 α1 (COL1A1), a protein in the periodontal ligament, in elderly individuals compared with younger individuals. Together, these findings indicate that an age-associated decrease in collagen in periodontal ligament is caused by epigenetic modifications, thus showing that epigenetic modifications may constitute as a risk factor for periodontitis.

Bacteria

Several studies suggested an association between oral bacteria and genetics. Certain polymorphisms found in the IL-6 genes in patients with severe periodontitis were found to be consistent with the presence of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* (35). These findings suggest that a certain genotype may be associated with a specific

composition of subgingival bacteria, thereby influencing disease susceptibility. Epigenetic modifications may influence periodontal pathogens, because an aberrant methylation mechanism was found to alter the virulence of *A. actinomycetemcomitans* by decreasing the ability of the bacteria to invade oral epithelial cells (36). However, pathogens in the oral mucosa may also cause epigenetic changes in the host. 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 1 (MDR1). It was suggested that an abnormal methylation might be triggered by inflammation (37). A maternal infection using the periodontal bacteria *Campylobacter rectus* (*C. rectus*) affected the methylation pattern of the *Igf2* gene, resulting in changes in the structure of the placenta in mice (38). In a previous study from our laboratory (39), we found an association between lipopolysaccharide (LPS) stimulation and epigenetic changes in histones in the IL-10 promoter, which further influenced the IL-10 gene expression. These epigenetic changes were also found to differ between IL-10 genotypes. Thus, this shows that the presence of bacteria may lead to epigenetic modifications that further influence the progression of disease. These findings are in line with the results presented by Oliviera *et al.* (40) who found that the IL-8 promoter was more methylated in periodontally healthy individuals compared with periodontitis patients. The authors concluded that inflammation in the oral mucosa induces changes in the DNA methylation pattern in the IL-8 gene in epithelial cells. This indicates a chronic inflammation such as periodontitis that may induce epigenetic modifications in the oral mucosa. In another study by the same group (41), the methylation pattern of the Toll-like receptor (TLR) two and four was investigated in gingival tissue. The results showed unmethylation of TLR4 in both the control group and the periodontitis group, while the TRL*2* gene showed both unmethylated and methylated DNA in all groups investigated. However, in their discussion, the authors indicated the possibility that some sites of the genes may present an aberrant methylation level in inflamed tissues.

Inflammation

Today, the mechanisms or factors causing gingivitis to develop into a tissue-destructive periodontitis are not fully understood. It has been suggested that an individual's genotype and its immunological defence against bacteria determine susceptibility for developing chronic periodontitis (42). In a study on patients with systemic lupus erythematosus (SLE), hypomethylation was found in the promoter region of the IL-4 and IL-6 genes. A concomitant increase in gene expression in T cells was also reported in these patients (43). The authors of the study referred to suggested that an increase in cytokine expression and pathological T cells might be a result of spontaneous demethylation in certain cytokines. Alterations in the epigenetic pattern have also been found in rheumatoid arthritis (RA) (44). Together, these findings indicate that chronic inflammatory processes may be a result of a decrease in histone deacetylase activity as well as changes in methylation, which subsequently leads to an increase in gene expression of inflammatory factors.

Most of the literature on epigenetics and inflammation is related to tumorigenesis and cancer development. The recently introduced concept of cancer immunoediting referring to the interactions between the immune system and dysplastic cells/tumour cells (45) supports the current view of chronic inflammation as a risk factor in the progression of tumour development (46, 47). Epigenetics was suggested as a potential link between inflammation and cancer (47). This is in line with the results presented by Huang *et al.* (48) who found an increase in methylation in the E-cadherin gene after *Helicobacter pylori* (*H. pylori*) stimulation. The mechanism suggested was that *H. pylori* causes an increase in IL-1β production, which then influences NFκB gene transcription, and a subsequent increase in DNA methyltransferase (DNMT) activity. An increase in DNMT activity leads to hypermethylation in the E-cadherin promoter region. The methylation pattern of E-cadherin was further investigated in patients with breast cancer as well as in patients with periodontitis (12). In comparison between the two patient groups with healthy controls, an increase in methylation was found in both patient groups compared with the control group. Furthermore, IL-6-induced chronic inflammation may lead to hypermethylation of tumour suppressor genes. This was suggested to be a factor contributing to the development of oral squamous cell carcinoma (49). Zhang *et al.* (50) investigated epigenetic modifications in periodontitis patients. The results showed a fivefold increase in methylation of the prostaglandin-endoperoxide synthase 2 (PTGS2) gene in gingival tissue samples from patients with periodontitis compared with samples from healthy controls. The increase in methylation in the regulatory part of the PTGS2 promoter was suggested to interfere with NFκB binding, resulting in a change in NFκB activity. Additional studies have investigated methylation status of cytokines in gingival tissue samples and oral epithelial cells, respectively (40, 51). The findings in these studies indicate that changes in the methylation pattern in promoter region of genes involved in inflammation may be caused either by the presence of periodontal pathogens or by the inflammatory process.

Periodontitis have several features in common with autoimmune diseases, for example RA and Sjögren's syndrome. One is the presence of larger numbers of B lymphocytes in patients compared with healthy control (reviewed in (52). B lymphocytes are important antigen-presenting cells in the host response to bacteria but can also produce cytokines that promote a chronic inflammation. In the study by Fraga *et al.* (18), a marked difference in both DNA methylation and histone acetylation in lymphocytes was found in older twins. This indicates a potential link between changes in epigenetics and chronic inflammation such as periodontitis and raises the question whether older periodontitis patients have the same epigenome in the inflammatory lesion as younger patients.

Treatment

As it has been suggested in the literature that epigenetic changes may influence disease susceptibility and progression, one may speculate that this could open up for new treatment models reversing these changes. The DNA methylation inhibitor S110 was found to dampen tumour progression in mice even though the size of the tumour did not decrease. A decrease in the tumour suppressor gene p16 expression was also reported (53). Even though most studies regarding epigenetics as new treatment models are related to DNA methylation, there are some studies on the use of HDAC inhibitors in treatment for cancer and RA (54, 55). In research on RA, several studies have demonstrated differences in HDAC activity in patient groups, and the results of animal experiments show a potential use of HDAC inhibitors in disease progression. However, it is difficult to conclude that the effects of these substances are only the effects of changes in epigenetic patterns (56, 57). The HDAC inhibitor HDAC42 was found to cause not only cell death of cancer cells *in vitro* but also a decrease in tumour growth and a prolonged survival in mice (54). Two other HDAC inhibitors, phenylbutyrate and trichostatin A (TSA), up-regulated the expression of p16 and p21 in synovial cells (55). The results indicated a correlation between histone hyperacetylation and anti-inflammatory mechanisms after treatment with these HDAC inhibitors.

Future research

The studies discussed in this article indicate that epigenetic modifications caused by smoking, diet, bacteria and inflammation affect the oral health and may contribute not only to disease susceptibility but also to response to treatment. The aetiology of the effects of smoking on the development and severity of periodontitis is still relatively unknown, as presented by Haffajee and Socransky (17). Epigenetics could be the link between the genome and the environment and perhaps provide new data on patient susceptibility. Finding the links between inflammation and cancer is currently a research focus, and studies have shown that inflammatory mechanisms and factors influence the development and progression of cancer. Therefore, investigation into epigenetic patterns in the oral mucosa may provide new treatment models not only for periodontitis but also for other oral diseases.

Epigenetic modifications are tissue specific, and therefore, analysis of epigenetic modifications in the oral mucosa is of great importance to gain knowledge of the effect of these mechanisms on oral health. Collecting tissue biopsies and/or blood samples could lead to complications for the patient. However, there are methods for collection of DNA in the oral cavity that are not invasive and could be performed by, for example, the dental hygienist, in a dental setting. Kusumoto *et al.* (58) demonstrated that DNA from oral rinses could be used for determining both DNA methylation status and histone modifications. Two other methods using buccal swabs and wooden spatula, respectively, have also been reported (59, 60). Bjornsson *et al.* (61) suggested a model for improving the explanation/aetiology of a complex disease and how genetic and epigenetic mechanisms may be analysed in future. The authors propose that the use of an 'epigenetic framework' may add to a disease explanation of three characteristics: age dependence, quantitative nature and the mechanism by which the environment changes the genetic predisposition to the disease. It was also suggested that the model might also be a tool to improve the power of epidemiological studies.

Future clinical studies using non-invasive techniques would provide data that are not only of importance to the individual patients but also from a health economic perspective for the society. An early identification of patients at risk of developing destructive periodontitis and an individual treatment plan directed to such susceptible patients may thus prevent disease progression and may also reduce costs for treatment and rehabilitation.

Conclusions

There is a void in the research on epigenetics in relation to oral health. Many studies have shown the importance of epigenetics in disease susceptibility and progression. Through these searches, we have identified some key factors, such as diet, smoking, environment, bacteria and inflammation, which may affect the oral health through epigenetic changes in genes involved in the immune response in the oral mucosa. Future clinical studies, performed by dentists and/or dental hygienists, could provide evidence if and how these factors affect the oral health. To prove a potential link between epigenetics and oral health would provide answers to why certain patients do not respond to treatment. In future, knowledge from these kinds of studies may be used to identify new treatment models for periodontitis and other diseases related to oral health. In addition, research in this field regarding local and genetic factors in the immune response may be used in diagnostics and in identifying individuals at risk of developing disease. As epigenetic patterns and modifications are reversible, this means that it can be modified by environmental factors and thereby lead to disease. It may also be possible to use this knowledge to reverse these changes, thereby inhibiting or preventing disease progression. Future clinical studies will need to investigate and assess whether environmental factors such as diet and smoking may influence epigenetic changes that can predispose to a disease.

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