Epigenetics in Dentistry

Diş Hekimliğinde Epigenetik

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ABSTRACT

The concept of epigenetics is gaining increasing attention because it can cause changes in phenotype without altering the DNA sequence and to be found to have a very effective role in the emergence of phenotypic variations and many diseases, as well as genetic factors. In comparison to the studies on the relationship of epigenetics with other systemic diseases in the field of medicine, studies on the place of epigenetics in dentistry are very few. However, studies on the relationship between epigenetic mechanisms and oral diseases and their effects on dentistry practice continue to increase and become popular day by day. It is tought to have effects on tooth formation and development, orthodontics, periodontal diseases and caries formation. In this review, the functioning of epigenetic mechanisms is explained and it is aimed to discuss the relationship of these mechanisms with tooth development and oral diseases. The relationship of epigenetic mechanisms with caries, which one of the most important diseases of childhood, and its effects tooth formation were especially evaluated. At the same time, current epigenetic-related studies and promising new treatment approaches for dentistry practice are included.

Keywords: *Epigenetic, genetics, dentistry*

ÖZ

Epigenetik kavramı, DNA dizisini değişikliğe uğratmadan fenotipte değişikliklere sebep olabilmesi ve fenotipik varyasyonlar ve birçok hastalığın ortaya çıkmasında genetik faktörlerin yanında oldukça etkili bir rolü olduğunun ortaya çıkarılması sebebiyle artan bir ilgi görmektedir. Epigenetiğin diş hekimliğindeki yeri ile ilgili yapılmış araştırmalar, epigenetiğin tıp alanındaki diğer sistemik hastalıklarla olan ilişkisi hakkında yaplan araştırmalara göre oldukça az sayıdadır. Fakat epigenetik mekanizmalar ile oral hastalıkların ilişkisi ve bu etkilerin diş hekimliği pratiği üzerine olan yansımaları hakkında yapılan çalışmalar gün geçtikçe artmaya ve popülerleşmeye devam etmektedir. Diş oluşumu ve gelişimi, ortotodonti, periodontal hastalıklar ve çürük oluşumu üzerinde etkileri olduğu düşünülmektedir. Bu derleme çalışmasında, epigenetik mekanizmaların işleyişi anlatılmış ve bu mekanizmaların diş gelişimi ve oral hastalıklarla olan ilişkisi ele alınması amaçlanmıştır. Epigenetik mekanizmaların çocukluk çağının en önemli hastalıklarından olan çürükle olan ilişkisi ve diş oluşumu üzerinde olan etkileri özellikle değerlendirilmiştir. Aynı zamanda epigenetik ile ilgili güncel çalışmalara ve diş hekimliği pratiği için umut vaat eden yeni tedavi yaklaşımlarına yer verilmiştir.

Anahtar Kelimeler: *Epigenetik, genetik, diş hekimliği*

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Defining Epigenetics

Epigenetics refers to stable differences in gene expression that can be transmitted through meiotic and/or mitotic divisions without altering DNA sequences.[1] In other words, it refers to heritable phenotypic variations that are not caused by changes in the DNA sequence.[2] In its latest epigenomic reports (2009), the National Institutes of Health (NIH) of the United States defined epigenetics as encompassing both heritable changes in gene activity and expression (within the lineage of cells or individuals) and stable, long-term modifications in the transcriptional potential of a non-heritable cell.[3] Genetics, on the other hand, is defined as the study of heritable variations in gene function or activity that are directly related to changes in the DNA sequence. Such changes include deletions, point mutations, translocations, and insertions.[4] While genetic mutations are irreversible, epigenetic modifications can be reversible.[1] In summary, the key difference between genetics and epigenetics is that epigenetic modifications can be reversed using chemical agents. Additionally, the exact mechanisms of epigenetic inheritance have not yet been fully elucidated.[5]

Epigenetics seeks to explain how dramatic phenotypic differences arise in cells and organisms that share the same DNA. Various dietary and environmental factors can influence the extent and scope of epigenetic effects to varying degrees. Findings from epigenetic research have also revealed intriguing correlations between lifestyle choices and disease risk, further supporting this phenomenon.[6]

Mechanisms of Epigenetic Regulation

The three fundamental mechanisms of epigenetics have been identified as DNA methylation, post-translational modification of histone proteins, and RNA-based mechanisms.[3,6] These mechanisms are responsible for initiating and maintaining epigenetic silencing and the regulation of gene expression profiles. They also form the foundation for various cellular processes, including gene expression, cell differentiation, embryogenesis, X chromosome inactivation, and genomic imprinting.[7,8] Uncovering the relationships between these components has facilitated a faster and more insightful understanding of the regulation of gene expression. However, changes in an epigenetic profile can have a significant impact on cellular function, potentially leading to dysregulation of gene expression and, as a result, the development of epigenetic diseases.[9]

Dentistry and Epigenetics

Despite the numerous studies published on epigenetics in biology and medicine, research on the impact of epigenetics in dentistry is fewer and more limited. Due to its role in gene expression during development and its potential to influence susceptibility to oral diseases, epigenetics is expected to become increasingly popular in the field of dentistry.[10]

Although much of the research has focused on the effects of negative life experiences, beneficial developments can also induce changes in the epigenome. While epigenetics currently does not have a practical application in dentistry, it is believed to offer significant benefits in the future. For this reason, it is emphasized that all clinical practitioners should be aware of the fundamental principles.[11] It is anticipated that epigenetics could enable early intervention for the prevention of periodontitis, potentially preventing hypodontia and various dental anomalies related to tooth development. Epigenetics is also predicted to serve as a reliable screening tool for various dental anomalies, including enamel defects, and as a means to assess an individual's susceptibility to dental caries or periodontal disease more efficiently.[11,12]

Tooth Formation and Development (Odontogenesis)

This process is primarily controlled by the genome. However, it is well-known that epigenetic factors have an undeniable impact on tooth formation. Previous studies have shown that external factors, such as environmental influences leading to hypo- and hypermethylation of DNA, can cause differences in the teeth of monozygotic twins. Additionally, abnormal epigenetic regulation can disrupt the tooth formation process, leading to dental malformations and agenesis.[13]

Tooth formation is a complex process that involves numerous molecular events within the signaling pathways between epithelial and neural crest-derived mesenchymal tissues, which often overlap and occur in succession. [14,15] Environmental factors (such as radiation, chemotherapy, medications, etc.) and genetic mutations that influence any stage of the process can impair or halt tooth development. This, in turn, may lead to abnormalities in the number, shape, size, and structure of the teeth.[16]

Hypodontia

Hypodontia refers to a dental anomaly that includes a range of heterogeneous phenotypes, from anodontia (absence of all teeth) to oligodontia, which involves the congenital absence of one or more teeth, excluding third molars, typically involving more than six missing teeth. It can often present either as part of a syndrome or as an isolated feature unrelated to any syndrome. In most cases, it is reported that only one or two teeth are affected.[17] It is believed that the interactions between environmental, genetic, and epigenetic factors during tooth formation may contribute to abnormalities, but the exact mechanisms of formation are not yet fully understood. It is now well-established that DNA methylation plays a significant role in abnormal development, the emergence of defective phenotypes, and diseases, and it is thought that this process may also be involved in such conditions.[18]

Tooth Number and DNA Methylation

DNA methylation and histone modifications are two of the most common epigenetic modification processes.[19] In other words, they are the most common changes observed in DNA. They regulate chromatin inactivation, specific gene expression associated with embryonic growth, cell differentiation, and cancer progression, as well as determining the spatial control of cells and the timing of signaling interactions.[20] It has also been found that an enzyme called Histone Demethylase plays a role in regulating the differentiation of dental stem cells.[21]

Tooth development is influenced by interactions between neural crest and ectodermal epithelial tissues, and the pathogenesis of tooth agenesis can be determined by the interaction of multiple genes, as well as epigenetic and environmental factors.[22] In the post-genomic era, the epigenetic perspective and its effects have gained significant attention in recent years, with increasing evidence suggesting that epigenetic regulation plays a crucial role in phenotypic determination. Similar to the classic ‘epigenetic landscape’ metaphor proposed by Waddington, a 2016 study also suggested that changes in DNA methylation could lead to subtle differences in the spatial and temporal expression of local signals in odontogenic cells. In response to this, the number of teeth could be affected, and through an amplification mechanism, significant differences in the final appearance of odontogenesis could arise.[23]

According to Waddington, the local tissue-level interactions observed between cells during tooth formation are believed to be an example of an epigenetic event. Studies on monozygotic twin pairs with missing or extra teeth support the role of epigenetic factors in the tooth development.[24] For example, in a study of 24 monozygotic twin pairs with congenital absence of upper incisors or second premolars, it was found that in 21 of the pairs, the number and position of the affected teeth were inconsistent. Additionally, in 8 out of 9 monozygotic twins, the number of extra teeth was also reported to be inconsistent.[25]

Another study conducted on nine Japanese individuals with cleidocranial dysplasia syndrome revealed significant variability in the expression of supernumerary teeth among individuals with the same genetic mutation. Additionally, the study demonstrated the presence of discordance in one pair of monozygotic twins.[26] These findings support the view that supernumerary tooth formation is influenced not only by genetic factors but also by environmental and epigenetic factors.[27]

Various factors can influence both the establishment of methylation and the maintenance of this methylation process over time. The factors studied and hypothesized so far include age, ethnicity, dietary characteristics, chemical exposure, and smoking.[25,27,28]

Periodontology

Cytokines are among the biomolecules that trigger the inflammatory response and are generally classified as pro-inflammatory and anti-inflammatory cytokines. Epigenetic modifications in genes encoding cytokines have been shown to alter cytokine expression, potentially leading to either pro-inflammatory or anti-inflammatory responses. Additionally, studies have demonstrated a relationship between epigenetic variations in genes responsible for encoding pro-inflammatory cytokines and periodontitis.[29] Epigenetic modifications in pro-inflammatory mediators in periodontitis are associated not only with oral bacteria but also with various environmental factors such as smoking and diet.[30,31] A relationship between DNA methylation, pro-inflammatory mediators, and aggressive periodontitis has been demonstrated.[32]

Orthodontics

Current studies in the periodontal field investigate the effects of known epigenetic mechanisms on specific genes, whereas orthodontic literature focuses on the broader scope of epigenetics, classifying environmental factors such as condylar forces that influence jaw growth and remodeling. From this perspective, environmental factors are not considered influences on the genome itself but rather external elements. Forces acting on the jaw can induce epigenetic changes that affect gene expression. However, orthodontic literature has yet to fully elucidate which specific epigenetic modifications influence which genes.[10]

Profitt highlights that a fundamental difference in craniofacial growth theory lies in the location where gene regulation is expressed.[33] For example, if bone is considered the primary determinant of craniofacial growth, genetic control is assumed to occur at the bone level. If cartilage is regarded as the key determinant, genetic regulation is thought to take place at the cartilage level. As explained in Moss’s Functional Matrix Hypothesis, if the matrix of soft tissues surrounding skeletal elements is considered the main determinant of bone development, then genetic control is believed to occur outside the skeletal system.[34]

Carlson has stated that he believes the genes regulating craniofacial development are switched on and off at critical time points. He argues that the key factor is not the control of morphogenesis by intrinsic factors within the genome, but rather the complex interactions between distant extrinsic factors in the body and environment, as well as the cells and tissues that trigger or inhibit gene expression influencing postnatal growth. These interactions, in turn, affect developmental processes and the rate of response to clinical treatment procedures.[35] Carlson suggested that, in the future, orthodontists might commonly use molecular kits to diagnose growth-related issues, assess each patient's developmental stage, and determine the presence or absence of key polymorphisms in growth factors and signaling molecules.[10,35]

Amelogenesis (Enamel Formation)

It is stated that tooth enamel is the hardest tissue known in the human body and develops from the oral epithelium. More than 95% of its volume is composed of large and organized hydroxyapatite crystals, making it a highly mineralized tissue. The formation of this highly organized and extraordinary structure is believed to be controlled by ameloblasts through the interaction of various organic matrix components containing enzymes such as tuftelin, enamelin, amelogenin, dentin sialophosphoprotein, matrix metalloproteinase 20, ameloblastin, amelotin, and kallikrein 4.[36] Ameloblasts, which are responsible for the production of enamel, undergo numerous differentiation processes during enamel formation. In the continuously erupting incisors, Sox2-positive cell populations are located in the labioservical loops of the enamel organs and contribute to the formation of all epithelial cells of the tooth, including ameloblasts, the stratum intermedium, stellate reticulum, and the epithelial cell remnants of the Malassez cells.[37,38]

Enamel formation consists of several developmental stages that are tightly regulated and controlled by interactions between the dental epithelium and mesenchymal tissue. Small alterations in these complex biochemical and physiological developmental processes can lead to significant enamel defects in terms of shape, color, and structure. It has been found that regulations in microRNA (miRNA), DNA methylation, and chromatin modifications act as key regulatory mechanisms in tooth development. The increasing number of studies on the epigenetic regulations involved in enamel development offers an exciting opportunity to identify new etiological factors related to enamel and explore potential therapeutic approaches.[39]

Immunohistochemical studies have shown that DNA Methyltransferase 1 (Dnmt1) is highly expressed in immature dental epithelial cells, with expression levels decreasing in later developmental stages, consistent with quantitative data published in a 2015 study. Additionally, de novo DNA methyltransferases Dnmt3a, Dnmt3b, and the TET family genes (with the exception of Tet1, which is highly expressed in immature dental epithelial cells) have been found to be predominantly expressed. The obtained spot staining data and immunohistochemical results suggest that dynamic changes in DNA methylation and hydroxymethylation occur during enamel formation. These findings indicate that Dnmt1 and Tet1 may be important epigenetic factors involved in enamel development.[40]

In the same study, immunohistochemical analysis of Dnmt1 in the developing mandibular incisors of 10-day-old mice revealed the presence of Dnmt1 in the cervical loop epithelium and surrounding pulp mesenchyme, with Dnmt1-positive cells disappearing as tooth development progressed. The stellate reticulum, outer enamel epithelium, other cells in the papillary layer, and stratum intermedium were also reported to stain exclusively with Dnmt1. Therefore, it is suggested that Dnmt1 may be associated with the undifferentiated state of dental epithelial cells. In summary, Dnmt and TET enzyme families appear to be key players in this epigenetic reprogramming. Consequently, it is hypothesized that changes in the chromatin structure of dental epithelial cells occur as DNA methylation progresses. This information is believed to be valuable in understanding the epigenetic events during enamel formation.[40]

Figure 1: Amelogenesis imperfecta can be clinically classified into various subtypes depending on the type of defect and the stage of enamel development at which it occurs. a-b-c-d: hypoplastic type, e-f: hypocalcified type, g-h: hypomature type.[36]

Enamel Defects

Amelogenesis Imperfecta (AI) is a congenital disorder that can affect the process of enamel formation and mineralization. In AI, the enamel of the teeth may present as hypomature (normal enamel thickness but colorless and softer than normal enamel), hypocalcified (normal enamel thickness but extremely weak), hypoplastic (thin enamel), or combinations of these variations.[41]

The normal development of dental enamel occurs in three stages. In the first stage, the matrix of the enamel is formed. In the second stage, the matrix undergoes the process of mineralization, and in the third stage, crystal growth leads to maturation. Enamel formation in permanent incisors begins between the ages of 3 and 12 months and is completed by the age of 4 to 7 years.[37,38]

The presence of enamel defects is closely associated with events occurring during the critical stages of enamel formation and mineralization. Enamel defects are linked to a wide range of causes, including genetic and epigenetic factors, as well as systemic, local, and environmental influences. Perinatal or prenatal conditions, low birth weight, routine antibiotic use, malnutrition, systemic diseases such as celiac disease, and respiratory disorders such as asthma can be associated with enamel defects[39]

Environmental factors known to affect enamel formation include fever, hypoxia, malnutrition, and exposure to various toxic substances that adversely affect enamel cells during development. Other influencing factors include environmental pollutants and socioeconomic status. During the time when cells are secreting the enamel, these external factors can interfere with the formation of enamel.[39]

Molar Incisor Hypomineralization (MIH) is another clinical condition that demonstrates the potential impact of environmental factors on enamel formation. In the presence of a genetic predisposition, medical issues that arise during various prenatal, perinatal, and postnatal periods, the use of certain medications in early life, and early exposure to fluoride and environmental pollutants (such as dioxins, polychlorinated biphenyls or PCBs) can lead to hypomineralization of the dental enamel.[40]

Respiratory diseases such as asthma can make ameloblasts highly sensitive to oxygen supply. The use of toothpaste containing mint can also lead to shortness of breath, increasing bronchospasm and potentially causing ameloblastic anoxia. The prevalence of enamel hypoplasia in children with bronchial asthma is significantly higher compared to children without the disease.[42] It has been found that the prevalence of enamel defects in permanent teeth among Brazilian children with asthma is 11 times higher compared to normal children.[43,44] Respiratory diseases like these have been associated with limited opacification and developmental defects observed in the enamel structure of the first permanent molars.[38]

Figure 2: Enamel hypoplasia and defects in the anterior and posterior teeth of a patient with a history of asthma medication use.[38]

Dentin Formation and Defects

Dentin formation is a highly organized and regulated process that involves multiple cellular and extracellular components. Interactions between various factors occur during the differentiation and morphogenesis stages; however, they can also take place during the mineralization phase of the extracellular matrix in dentin. The subsequent mineralization process in dentin formation shows some similarities with osteogenesis and cementogenesis.[45]

The dentinogenesis process, including odontoblast differentiation, is stated to be based on the coordinated expression of regulatory genes such as transcription factors and growth factors. Gene expression is influenced by epigenetic conditions such as DNA methylation and histone modifications. DNA methylation has been found to regulate odontoblast differentiation. However, the effects of histone modifications on the control of odontoblast differentiation are not yet fully understood. Nevertheless, published in vitro studies confirm that histone acetylation plays a role in dentin formation.[46]

A study published in 2020 investigated the expression patterns of histone proteins, specifically histone 3 lysine 9 (H3K9ac) and H3K27ac, during dentinogenesis and odontoblast differentiation. Using mandibular incisors from live mice, the study showed that H3K27ac and H3K9ac were up-regulated during odontoblast and dentinogenesis differentiation. The research also observed that histone acetyltransferases (HATs), p300, and histone deacetylase 3 (HDAC3) exhibited a distinct expression pattern during differentiation. Furthermore, it was confirmed that histone acetyltransferases, p300, and HDAC3 modulate histone acetylation and regulate odontoblast differentiation. The coordinated expression of p300 and HDAC3 was found to be up-regulated by histone acetylation in order to regulate dentin formation.[46]

Behavior Management

It has long been known that a mother's fear of the dentist is a significant factor in some children's anxiety and issues with accepting dental care.[47] Evidence showing that fear is transmitted across generations at behavioral, neuro-anatomical, and epigenetic levels suggests that dental anxiety likely has deeper causes, as some anxious children are more likely to adopt behaviors learned from their parents. This implies that for certain children, treatment should aim not only at addressing learned fears but also at identifying epigenetic changes. According to Yehuda and colleagues' research, psychotherapy can create an 'environmental regulation' model that can alter epigenetic states. The study demonstrated that psychotherapy affects the activity of stress hormones and alters the methylation of the FKBP5 gene in a specific region of DNA. Additionally, the study found that methylation of the GR gene (NR3C1) at the exon 1F promoter influenced treatment outcomes. These findings suggest that epigenetic testing could be developed to predict which patients with behavioral issues will respond to psychotherapy, and successful treatment outcomes could be associated with epigenetic changes. [10,48]

Childhood Caries and Epigenetics

Despite significant progress over the years in caries management, including the protective effects of fluoride, increased oral health activities, comprehensive health education, and advancements in treatment options, dental caries remains the most prevalent childhood disease.[49] There is direct evidence suggesting that genetic components play a role in the etiology of dental caries, but very little is known about the specific mechanisms involved.[50,51] There are numerous genes related to hereditary changes that affect the composition and structure of enamel, as well as genes involved in the genetic regulation of salivary gland functions and sugar metabolism. However, it cannot be said that there is a single host gene directly responsible for initiating or regulating dental caries progression.[19,52]

Epigenetics is a biological process that interacts with gene sequences (or DNA) to modify gene expression through molecular mechanisms. Events occurring in the early stages of life can influence the disease risk in the developing fetus.[53] Although few studies have explored this connection, epigenetic changes may increase the risk of dental caries by altering the expression of genes related to enamel formation, taste, immunity, and saliva secretion, likely as a response to adverse events during pregnancy and early life.[19]

Maternal obesity has been linked to obesity in childhood. Shared nutrition and lifestyle choices are significant factors in this relationship; however, 'fetal programming' can also contribute to this condition due to its epigenetic effects on the intrauterine environment.[54] However, despite numerous studies showing a correlation, the link between obesity and dental caries remains a controversial topic.[55]

A birth cohort study involving 27 male twins was conducted in 2021 to investigate the relationship between DNA methylation in leukocytes obtained from umbilical cord blood at birth and dental caries experience and dental enamel hypomineralization at age 6. The 6-year dental examination assessed (i) 'any caries' (untreated and treated caries), (ii) 'advanced caries' (untreated, advanced caries and/or previous treatment), and (iii) the presence/absence of hypomineralized second primary molars (HSPM). The study also considered whether the twins were monozygotic or dizygotic. Differentially methylated regions (DMR) and CpGs (DMCpG) were examined. The results showed that 19 children had 'no caries' while 15 had 'advanced' caries and 18 had HSPM. DMCpGs were not associated with 'any caries' but 16 and 19 DMCpG genes were found to be associated with 'progressive caries' and HSPM, respectively. DMR was found to be associated with all three outcomes. The genes associated with these analyses include PBX1, ACAT2, LTBP3, and DDR1, which have been linked to dental tissue development in genetic studies. These findings suggest that epigenetic differences present at birth may be associated with dental health at age 6, and these differences may serve as an important biomarker of early dental health effects.[56]

Current Approaches Related to Epigenetics

Epigenetic changes involve various histone and DNA modifications that can lead to significant phenotypic alterations. These epigenetic events are inherently reversible. In response to secondary environmental changes, epigenetic modifications can progress further, be reversed, and even completely restore the substrate to its original state, demonstrating a capacity for full reversal.[57]

Recent studies have shown that histone modifications are associated with the methylation of CpG nucleotides within DNA, thereby linking a wide range of epigenetic modifications and regulatory mechanisms.[58] This connection creates new scenarios in which an 'epigenetic code' can control the expression of specific gene sequences, essentially acting as an 'on/off' switch for numerous cellular events. As epigenetic drugs continue to be developed and become more refined and specific, greater control over epigenetic switches will be possible. If an appropriate therapeutic combination can be developed, it may be possible to reverse disease phenotypes, especially when drugs are applied during the early stages of the disease. For example, the idea that epigenetic drugs could eliminate resistant cancer cells while preventing the formation of cancer precursor cells is being explored.[59]

Epigenetic modifications are responsible for differentiating the expression of our genetic material in terms of time and space. This helps explain why, despite all our cells having the same DNA, such a wide variety of cell types can form different tissues and perform distinct functions. Most studies focus on the effects of negative life experiences, but positive events can also induce changes in the epigenome, some of which can be reversed.[48]

Through research on epigenetics, several key factors that may affect oral health, including diet, smoking, environment, bacteria, and inflammation, have been identified as potentially influencing immune responses. Future clinical studies conducted by dentists and dental hygienists will provide insights into whether and how these factors affect oral health.[60]

The potential link between epigenetics and oral health will also provide answers as to why some patients do not respond to treatment. Furthermore, studies on genetic and local factors in immune responses can be used to identify and diagnose individuals at risk of developing disease. Since epigenetic changes are reversible, it should not be overlooked that these changes can be altered by environmental factors, potentially leading to disease. From this perspective, reversing epigenetic changes and preventing or halting the progression of disease will become possible.[60]

It is now known that various nutritional factors, such as folic acid, vitamin B12, and vitamin A, can cause changes in epigenetic modifications. Additionally, it has been stated that smoking can lead to changes in DNA through effects such as hypomethylation and hypermethylation. Therefore, it is emphasized that certain exogenous factors, including diet, smoking, environment, bacteria, inflammation, and age, can trigger epigenetic changes that affect oral health.[60]

Current Diagnostic and Therapeutic Approaches in the Field of Periodontology

Current international consortia are increasingly emphasizing the importance of the relationship between general health and oral health. There is a growing trend of epigenetic research in dentistry, and numerous epigenetic studies have begun in the field of periodontology. In addition to microbial communities, one of the environmental factors, interactions between pathogens and the host also play a significant role in the control of periodontal diseases. Since genetic factors are insufficient to explain the variation in host responses, epigenetic effects have been suggested to explain these differences. While genetic factors are undoubtedly crucial in the development of the disease, they can become risk factors when the body is triggered by something foreign. However, epigenetic changes can alter gene expression patterns by inducing different host responses without changing the DNA sequence. Therefore, research has focused on controlling disease susceptibility to infections through gene expression, immune responses, and epigenetic factors. Additionally, studies are ongoing to discover new epigenetic biomarkers for diagnosis, prognosis, and treatment methods.[61]

Various epidemiological findings demonstrate a close relationship between non-communicable diseases and oral diseases. Additionally, there is a possibility of overlap in common risk factors between systemic and oral diseases and epigenetics. In parallel with global research, further investigation into the functional and regulatory factors associated with periodontal health status and systemic diseases will help identify new biological mechanisms, thus aiding in the development of diagnostic biomarkers and therapeutic strategies to support both oral and systemic health.[62]

Current Diagnostic and Treatment Approaches Related to Pulp Inflammation

There are studies investigating the use of circulating miRNAs as biomarkers for several common inflammatory diseases (e.g., asthma, inflammatory bowel disease, rheumatoid arthritis).[63] Recent research has focused on the use of proteins as diagnostic biomarkers. In particular, the increased stability of miRNAs in the circulatory system offers enhanced diagnostic advantages, making them promising biomarkers for the diagnosis of pulpal conditions. Moreover, the recent increase in knowledge about miRNA biomarkers has introduced numerous new possibilities for the more accurate diagnosis of pulp diseases.[64]

The ability to isolate miRNAs from inflamed dental pulp samples or point-of-care diagnostic kits could enable accurate diagnosis and the selection of appropriate treatment procedures. This advancement has the potential to eliminate many of the clinical prediction methods currently used in dentistry. Additionally, the application of miRNA-based therapeutic dental materials to exposed pulp tissue is being considered to stimulate the differentiation of dental pulp stem cells into odontoblast-like cells and facilitate the initiation of dental pulp repair processes. Research on approaches involving non-coding RNA (ncRNA) is relatively new, and its integration into clinical practice will inevitably take time. These studies are creating exciting new research avenues in regenerative endodontics and are expected to be a focal point for future investigations.[64]

CONCLUSION

Epigenetic approaches reveal that the development of systemic diseases, oral diseases, and various phenotypic variations is not solely influenced by genetic factors. Numerous studies have shown that various environmental factors, diet, and other exogenous factors can cause changes in epigenetic modifications.[61] At the same time, many studies have demonstrated the role of epigenetic modifications in enamel formation, dentin formation, and related defects.[39,46]

The research is important because it shows that negative experiences, such as fear of the dentist, can be transmitted to the next generation through epigenetic inheritance, which is also relevant for clinical practices in dentistry.[48] Currently, the number of studies examining epigenetic approaches in dentistry remains insufficient. In the field of dentistry, further research is needed for epigenetic mechanisms to provide practical benefits to dentists in diagnosis, treatment, and clinical applications.

REFERENCES

1. Carrell D. Epigenetics of the male gamete. *Fertility and Sterility*. 2012;97(2):267-274.
2. Martin C, Zhang Y. Mechanisms of epigenetic inheritance. *Current Opinion in Cell Biology*. 2007;19(3):266-272.
3. Gibney E, Nolan C. Epigenetics and gene expression. *Heredity*. 2010;105:4-13.
4. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2013;38(1):23–38.
5. Özdemir F. Kolerektal Kanserli Hastalarda SFRP1 Geninin Araştırılması, Yüksek Lisans Tezi, İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü, 2019, İstanbul.
6. Hamilton JP. Epigenetics: principles and practice. *Digestive diseases*. 2011;29(2):130-135.
7. Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development. *Science*. 1975;187(4173):226-232.
8. Riggs AD, X inactivation, differentiation, and DNA methylation. *Cytogenet CellGenet*.1975; 14(1):9-25.
9. Zhang L, Lu Q, Chang C. Epigenetics in Health and Disease. *Epigenetics in Allergy and Autoimmunity*. 2020;978-981-15-3449-2.
10. Williams S, Hughes T, Adler C, Brook A, Townsend G. Epigenetics: a new frontier in dentistry. *Australian Dental Journal*. 2014;59(1);23-33.
11. Alvarez-Buylla ER, Chaos A, Aldana M, Benítez M, Cortes-Poza Y, Espinosa-Soto C, Hartasánchez DA, Lotto RB, Malkin D, Escalera Santos GJ, Padilla-Longoria P. Floral morphogenesis: stochastic explorations of a gene network epigenetic landscape. *PLoS One*. 2008;3(11):e3626.
12. Townsend GC, Brook AH. The face, the future, and dental practice: how research in craniofacial biology will influence patient care. *Aust Dent J*. 2014;59(1):1-5.
13. Li C, Cui Y, Zhou C, Sun J, Zhou X. Epigenetics in Odontogenesis and its Influences. *Curr Stem Cell Res Ther*. 2018;13(2):110-117.
14. Xiao L, Tsutsui T. Three-dimensional epithelial and mesenchymal cell co- cultures form early tooth epithelium invagination-like structures: expression patterns of relevant molecules. *Journal of cellular biochemistry*. 2012;113(6):1875-1885.
15. Rothová M, Peterková R, Tucker AS. Fate map of the dental mesenchyme: dynamic development of the dental papilla and follicle. *Developmental biology*. 2012;366(2):244-254.
16. Goldenberg M, Das P, Messersmith M, Stockton DW, Patel PI, D'Souza RN. Clinical, radiographic, and genetic evaluation of a novel form of autosomal-dominant oligodontia. *J Dent Res.* 2000;79(7):1469-1475.
17. Bailleul-Forestier I, Molla M, Verloes A, Berdal A. The genetic basis of inherited anomalies of the teeth. Part 1: clinical and molecular aspects of non-syndromic dental disorders. *European journal of medical genetics.* 2008;51(4):273-291.
18. Wang J, Sun K, Shen Y. et al. DNA methylation is critical for tooth agenesis: implications for sporadic non-syndromic anodontia and hypodontia. *Scientific reports.* 2006;6:19162.
19. Barros SP, Offenbacher S. Epigenetics: connecting environment and genotype to phenotype and disease. *J Dent Res.* 2009;88(5):400-408.
20. Robertson KD, Wolffe AP. DNA methylation in health and disease. Nat Rev Genet. 2000;1(1):11-19.
21. Brook AH. Multilevel complex interactions between genetic, epigenetic and environmental factors in the aetiology of anomalies of dental development. *Arch Oral Biol.* 2009;54(1):3-17.
22. Koussoulakou DS, Margaritis LH, Koussoulakos SL. A curriculum vitae of teeth: evolution, generation, regeneration. *Int J Biol Sci.* 2009;5(3):226-243.
23. Waddington CH. The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology. *Medical Journal of Australia*. 1957;1(15):493-493.
24. Townsend G, Hughes T, Luciano M, Brook A. Genetic and environmental influences on human

dental variation: limitations and advantages of studies involving twins. *Arch Oral Biol*. 2009;54(1):45-51.

25. Townsend GC, Richard L, Hughes T, Pinkerton S, Schwerdt W. Epigenetic influences may explain dental differences in monozygotic twin pairs. *Australian dental journal*. 2005;50(2);95-100.
26. Suda N, Hattori M, Kosaki K, Banshodani A, Kozai K, Tanimoto K, Moriyama K. Correlation between genotype and supernumerary tooth formation in cleidocranial dysplasia. *Orthod Craniofac Res*. 2010;13(4):197-202.
27. Townsend G, Bockmann M, Hughes T, Brook A. Genetic, environmental and epigenetic influences on variation in human tooth number, size and shape. *Odontology*. 2012;100(1):1-9.
28. Hughes TE, Townsend GC, Pinkerton SK, Bockmann MR, Seow WK, Brook AH, Richards LC, Mihailidis S, Ranjitkar S, Lekkas D. The teeth and faces of twins: providing insights into dentofacial development and oral health for practising oral health professionals. *Aust Dent J.* 2014;59(1):101-16.
29. Zhang S, Barros SP, Moretti AJ, Yu N, Zhou J, Preisser JS, Niculescu MD, Offenbacher S. Epigenetic regulation of TNFA expression in periodontal disease. *J Periodontol*. 2013;84(11):1606-16.
30. Zhang S, Barros SP, Niculescu MD, Moretti AJ, Preisser JS, Offenbacher S. Alteration of PTGS2 promoter methylation in chronic periodontitis. *J Dent Res.* 2010;89(2):133-7.
31. Ohi T, Uehara Y, Takatsu M, Watanabe M, Ono T. Hypermethylation of CpGs in the promoter of the COL1A1 gene in the aged periodontal ligament. J *Dent Res*. 2006;85(3):245-50.
32. Andia DC, de Oliveira NF, Casarin RC, Casati MZ, Line SR, de Souza AP. DNA methylation status of the IL8 gene promoter in aggressive periodontitis. *J Periodontol*. 2010;81(9):1336-41.
33. Proffit WR, Fields HW, Sarver DM. Contemporary orthodontics. 5th edn. Elsevier-Mosby, St Louis. 2012;978-0-323-083-17-1.
34. Iacopino AM. Epigenetics: new explanations for old problems? *Journal (Canadian Dental Association*) 2010;76(1):a76.
35. Carlson DS. Theories of craniofacial growth in the postgenomic era. Seminars in Orthodontics. 2005;11(4):172-183.
36. Crawford PJ, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. *Orphanetjournal of rare diseases*. 2007;2:17.
37. Harada H, Kettunen P, Jung HS, Mustonen T, Wang YA, Thesleff I. Localization of putative stem cells in dental epithelium and their association with Notch and FGF signaling. *J Cell Biol*. 1999;147(1):105-20.
38. Juuri E, Saito K, Ahtiainen L, Seidel K, Tummers M, Hochedlinger K, Klein OD, Thesleff I, Michon F. Sox2+ stem cells contribute to all epithelial lineages of the tooth via Sfrp5+ progenitors. *Dev Cell*. 2012 Aug 14;23(2):317-328.
39. Fan Y, Zhou Y, Zhou X, Xu X, Pi C, Xu R, Zheng L. Epigenetic Control of Gene Function in Enamel Development. *Curr Stem Cell Res Ther*. 2015;10(5):405-411.
40. Yoshioka H, Minamizaki T, Yoshiko Y. The dynamics of DNA methylation and hydroxymethylation during amelogenesis. *Histochem Cell Biol.* 2015;144(5):471-478.
41. Kim YJ, Lee Y, Kasimoglu Y, Seymen F, Simmer JP, Hu JC, Cho ES, Kim JW. Recessive Mutations in ACP4 Cause Amelogenesis Imperfecta. *J Dent Res*. 2022;101(1):37-45.
42. Pinkham J, Casamassimo P, McTtigue D, Fields H, Nowak A. Pediatric dentistry: Infancy through adolescence. Saunders (An imprint of Elsevier), St. Louis. 2005; 978- 0721603124.
43. Guergolette RP, Dezan CC, Frossard WT, Ferreira FB, Cerci Neto A, Fernandes KB. Prevalence of developmental defects of enamel in children and adolescents with asthma. *J Bras Pneumol*. 2009;35(4):295-300.
44. Jälevik B, Norén JG, Klingberg G, Barregård L. Etiologic factors influencing the prevalence of demarcated opacities in permanent first molars in a group of Swedish children. *Eur J Oral Sci*. 2001;109(4):230-234.
45. Linde A, Goldberg M. Dentinogenesis. *Critical Reviews in Oral Biology & Medicine*.1993; 4(5):679-728.
46. Tao H, Li Q, Lin Y, Zuo H, Cui Y, Chen S, Chen Z, Liu H. Coordinated expression of p300 and HDAC3 upregulates histone acetylation during dentinogenesis. *J Cell Biochem*. 2020;121(3):2478-2488.
47. Sander K, Brook AH. A study of children who presented management problems for routine dental treatment. *J Int Ass Dent Child*. 1974;5:17-26.
48. Yehuda R, Daskalakis NP, Desarnaud F, Makotkine I, Lehrner AL, Koch E, Flory JD, Buxbaum JD, Meaney MJ, Bierer LM. Epigenetic Biomarkers as Predictors and Correlates of Symptom Improvement Following Psychotherapy in Combat Veterans with PTSD. *Front Psychiatry*. 2013;4:118.
49. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of untreated caries: a systematic review and metaregression. *J Dent Res*. 2015;94(5):650-8.
50. Shaffer JR, Wang X, McNeil DW, Weyant RJ, Crout

R, Marazita ML. Genetic susceptibility to dental caries differs between the sexes: a family-based study. *Caries Res*. 2015;49(2):133-40.

51. Olszowski T, Adler G, Janiszewska-Olszowska J, Safranow K, Kaczmarczyk M. MBL2, MASP2, AMELX, and ENAM gene polymorphisms and dental caries in Polish children. Oral Dis. 2012;18(4):389-95.
52. Shuler CF. Inherited risks for susceptibility to dental caries. *J Dent Educ*. 2001;65(10):1038-45.
53. Moore TG, Arefadib N, Deery A, West S. The First Thousand Days: An Evidence Paper. Parkville, Vic.: Centre for Community Child Health, Murdoch Children's Research Institute, 2017. p.6.
54. Wu Q, Suzuki M. Parental obesity and overweight affect the body-fat accumulation in the offspring: the possible effect of a high-fat diet through epigenetic inheritance. *Obes Rev*. 2006;7(2):201-8.
55. Hayden C, Bowler JO, Chambers S, Freeman R, Humphris G, Richards D, Cecil JE. Obesity and dental caries in children: a systematic review and meta-analysis. *Community Dent Oral Epidemiol*. 2013;41(4):289-308.
56. Mj S, N M, Jm C, Dj M, R S, Mc S, Dp B, J L, Nm K, Jl H, Kj S, S L. DNA methylation in childhood dental caries and hypomineralization. *J Dent.* 2022;117: 103913.
57. Heerboth S, Lapinska K, Snyder N, Leary M, Rollinson S, Sarkar S. Use of epigenetic drugs in disease: an overview. *Genet Epigenet*. 2014;6:9-19.
58. Sarkar S, Horn G, Moulton K, Oza A, Byler S, Kokolus S, Longacre M. Cancer development, progression, and therapy: an epigenetic overview. *Int J Mol Sci*. 2013;14(10):21087-21113.
59. Mataga MA, Rosenthal S, Heerboth S, Devalapalli A, Kokolus S, Evans LR, Longacre M, Housman G, Sarkar S. Anti-breast cancer effects of histone deacetylase inhibitors and calpain inhibitor. *Anticancer Res.* 2012;32(7):2523-2529.
60. Lod S, Johansson T, Abrahamsson K, Larsson L. The influence of epigenetics in relation to oral health. *International Journal of Dental Hygiene*. 2013;12(1):48-54.
61. Lindroth AM, Park YJ. Epigenetic biomarkers: a step forward forunderstanding periodontitis. J Periodontal *Implant Sci*. 2013:43;111-120.
62. Cho YD, Kim WJ, Ryoo HM, Kim HG, Kim KH, Ku Y, Seol YJ. Current advances of epigenetics in periodontology from ENCODE project: a review and future perspectives. *Clin Epigenetics*. 2021;13(1):92.
63. Mi S, Zhang J, Zhang W, Huang RS. Circulating microRNAs as biomarkers for inflammatory diseases. *Microrna.* 2013;2(1):63-71.
64. Kearney M, Cooper PR, Smith AJ, Duncan HF. Epigenetic Approaches to the Treatment of Dental Pulp Inflammation and Repair: Opportunities and Obstacles. *Frontiers ingenetics*. 2018;9:311.