International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

The Role of Peri-Implant Epigenetics: Emerging Insights into Osseointegration and Peri-Implantitis Susceptibility – A Review

Dr. Aakash Chatterjee[1], Dr. Mrunmayee Atkare[2]

[1]Post-graduate student, Department of Periodontology, Bharati Vidyapeeth (Deemed to be University) Dental College and Hospital, Sangli, Maharashtra.
[2]Private practitioner, Pune, Mumbai.

Abstract

Background: Dental implants have revolutionized the rehabilitation of edentulous spaces, but their long-term success is contingent upon effective osseointegration and the prevention of peri-implant diseases. Emerging research highlights the role of epigenetic modifications—heritable, reversible changes in gene expression that occur without alterations in DNA sequence—in modulating these biological outcomes.

Objective: This review aims to provide a comprehensive overview of the current understanding of epigenetic mechanisms in osseointegration and peri-implantitis, with emphasis on their clinical relevance, therapeutic potential, and application in precision implantology.

Results: DNA methylation and histone acetylation patterns critically influence the transcription of osteogenic genes such as RUNX2, BMP2, and ALP. Aberrant epigenetic profiles—such as hypomethylation of IL-1β and TNF-α promoters—have been identified in peri-implantitis tissues. Experimental use of HDAC inhibitors and miRNA mimics (e.g., miR-146a) has demonstrated enhanced osseointegration and reduced inflammation in preclinical models. Salivary and GCF-based epigenetic assays show promise as predictive biomarkers.

Conclusion: Epigenetics represents a promising frontier in implant dentistry, offering opportunities for early diagnosis, personalized risk assessment, and targeted therapy. However, clinical translation is still in its infancy. Future research must focus on longitudinal human studies, development of non-invasive diagnostic platforms, and integration with omics technologies to unlock the full potential of epigenetic science in implantology.

Keywords: Epigenetics, Dental implants, Osseointegration, Peri-implantitis, DNA methylation, MicroRNA.

INTRODUCTION-

Dental implants have revolutionized the field of restorative dentistry by offering predictable and long-term rehabilitation for edentulous patients. However, despite high success rates, a subset of implants fails due to complications such as peri-implantitis or inadequate osseointegration [1]. While bacterial colonization and biomechanical factors are well-established contributors to implant failure, recent attention has shifted towards host-related molecular and genetic influences. Among these, epigenetics—

defined as heritable changes in gene expression without alterations in the DNA sequence—has emerged as a critical regulatory layer that may influence peri-implant tissue response [2].

Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs (including microRNAs) dynamically regulate the transcription of genes involved in inflammation, wound healing, and bone metabolism [3]. These mechanisms can be influenced by environmental and lifestyle factors such as smoking, systemic disease, stress, and diet—all of which are known risk factors for peri-implant disease [4]. Studies have shown that specific epigenetic patterns, such as the hypermethylation of inflammatory cytokine genes or altered expression of osteogenic regulators like RUNX2 and BMP2, can impact both the osseointegration process and the onset of peri-implantitis [5,6].

Although the application of epigenetics in oncology and systemic disease has been widely explored, its role in dental implantology remains under-investigated. Understanding how these molecular switches govern peri-implant tissue behavior may unlock novel diagnostic and therapeutic pathways, including the development of biomarkers for implant prognosis or epigenetic drugs that modulate host responses [7].

This review aims to systematically evaluate the current literature on the role of epigenetic modifications in dental implant success and failure, with a focus on their involvement in osseointegration and peri-implantitis. The goal is to highlight the emerging significance of epigenetic mechanisms in implant dentistry and identify gaps for future translational research.

Overview of Epigenetic Mechanisms

Epigenetics is defined as the study of heritable changes in gene expression that occur without alterations in the nucleotide sequence of DNA. These modifications orchestrate gene transcription through dynamic molecular switches, thereby regulating cellular behavior in response to environmental stimuli [8]. The epigenetic landscape plays a critical role in tissue homeostasis, inflammation, bone remodeling, and wound healing—all of which are key components in determining implant integration and survival [9]. The three major categories of epigenetic mechanisms are DNA methylation, histone modifications, and non-coding RNAs. These mechanisms are not only interrelated but are also influenced by external factors such as smoking, systemic diseases (e.g., diabetes), stress, aging, and bacterial colonization [10].

DNA Methylation

DNA methylation involves the addition of a methyl group to the 5' position of cytosine rings within CpG dinucleotides, catalyzed by DNA methyltransferases (DNMTs). This epigenetic mark is typically associated with transcriptional repression when occurring in gene promoter regions. Methylation can stably silence genes during development or in response to inflammatory triggers.

In peri-implant tissues, aberrant DNA methylation has been linked to altered expression of genes involved in immune response and bone metabolism. For instance, hypermethylation of IL-10, an anti-inflammatory cytokine, has been observed in chronic inflammatory states, reducing its protective role in peri-implant tissues [11]. Similarly, methylation of promoters of osteogenic transcription factors such as RUNX2 and BMP2 has been associated with compromised osteoblastic differentiation and impaired osseointegration [12].

Conversely, hypomethylation of IL-1β, TNF-α, and MMP-9—genes critical in matrix degradation and inflammation—has been found in peri-implantitis lesions, promoting tissue destruction and alveolar bone resorption [13]. This highlights the dual role of DNA methylation: either promoting tissue stability or exacerbating breakdown depending on the genomic context and disease state.

Histone Modifications

Histone proteins form the core of nucleosomes and facilitate the compaction of DNA into chromatin. Post-translational modifications (PTMs) of histone tails—including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation—profoundly influence chromatin architecture and gene accessibility [14].

Histone acetylation, mediated by histone acetyltransferases (HATs), relaxes chromatin structure and enhances transcription, whereas histone deacetylases (HDACs) remove acetyl groups, leading to gene silencing. In bone biology, acetylation of histones near osteogenic genes like ALP, COL1A1, and OCN facilitates the transcription of genes required for mineralization and extracellular matrix formation [15]. Inhibition of HDACs using pharmacologic agents (e.g., valproic acid, trichostatin A) has shown promising results in promoting osteoblast differentiation and enhancing bone regeneration, suggesting a potential therapeutic strategy to improve osseointegration [16].

Histone methylation is more complex, as it can either activate or repress transcription depending on the lysine residue and the number of methyl groups added. For example, trimethylation of histone H3 at lysine 4 (H3K4me3) activates transcription, while trimethylation at H3K27 (H3K27me3) represses it. These histone marks regulate key transcription factors like Osterix and Runx2, which are central to osteoblast differentiation [17].

Non-Coding RNAs

Non-coding RNAs (ncRNAs) represent another major layer of epigenetic regulation. Among these, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have received particular attention in peri-implant biology.

MicroRNAs are short (~22 nucleotides) regulatory RNAs that bind to the 3' untranslated regions (3' UTRs) of target messenger RNAs (mRNAs), leading to translational repression or mRNA degradation. In the context of implant-related inflammation, miR-146a has emerged as a key suppressor of the NF-κB pathway by targeting IRAK1 and TRAF6, thereby downregulating the production of pro-inflammatory cytokines [18]. Similarly, miR-155 has been shown to mediate T-cell responses and promote inflammation in peri-implant mucosa [19].

In terms of bone regeneration, miR-29b and miR-21 are well-known to regulate osteoblast differentiation and matrix mineralization by targeting HDAC4 and PTEN, respectively [20]. These findings suggest that modulation of specific miRNAs could offer novel approaches for both managing peri-implantitis and enhancing osseointegration.

Long non-coding RNAs (lncRNAs), which are transcripts longer than 200 nucleotides, interact with chromatin-modifying complexes, transcription factors, or RNA-binding proteins to regulate gene expression at both transcriptional and post-transcriptional levels. Although still under investigation, lncRNAs such as HOTAIR and MEG3 have shown potential roles in regulating osteogenic differentiation and immune responses, which may have future implications in implantology [21].

Integrated Epigenetic Control

These three mechanisms often interact. For example, a miRNA may target an mRNA encoding a histone-modifying enzyme, or DNA methylation may silence a lncRNA gene. This crosstalk forms a complex regulatory network that governs peri-implant tissue dynamics. Disruption in this equilibrium—due to host

susceptibility or environmental factors—can tip the balance toward either regeneration or destruction, determining the fate of the implant

Epigenetics in Osseointegration

Osseointegration is the biological process by which a direct, functional connection is established between living bone and the surface of an implant. This process is multifactorial, requiring a well-regulated interplay of osteoblast and osteoclast activity, angiogenesis, immune modulation, and extracellular matrix formation. Recent advances in molecular biology suggest that epigenetic modifications critically influence these cellular behaviors, particularly in the early healing phase post-implantation.

Regulation of Osteoblast and Osteoclast Genes

Bone remodeling is tightly regulated by the differentiation and activity of osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Several epigenetic factors are involved in the transcriptional regulation of osteogenic transcription factors such as RUNX2, Osterix (SP7), and ALP, which are essential for osteoblast lineage commitment. Likewise, genes such as RANKL, NFATc1, and TRAP are crucial for osteoclastogenesis and are also subject to epigenetic regulation [22].

For example, DNA methylation of the RUNX2 promoter has been shown to suppress osteoblast differentiation. In contrast, demethylation promotes its transcription, enhancing osteogenesis around implant sites [23]. Similarly, histone acetylation has been reported to increase the transcription of ALP, COL1A1, and OCN, all of which are involved in bone matrix formation [24].

Key Epigenetic Factors Enhancing or Inhibiting Bone Formation

Histone deacetylase inhibitors (HDACis) such as valproic acid and trichostatin A have demonstrated the ability to promote osteogenic differentiation of mesenchymal stem cells (MSCs), both in vitro and in vivo, by increasing histone acetylation at osteoblast-related genes [25]. These agents enhance the transcription of BMP2, RUNX2, and SP7, improving mineralization and early implant stability [26].

MicroRNAs also contribute to bone formation. miR-29b enhances osteogenesis by downregulating negative regulators such as HDAC4 and TGF-β3, while miR-21 promotes osteoblast proliferation via PTEN/PI3K/AKT signaling [27]. On the other hand, miR-133a and miR-204 suppress osteogenesis by targeting RUNX2 mRNA, and their overexpression has been linked to poor osseointegration [28].

Epigenetic Markers Influencing Early Implant Healing

The early healing phase around implants is marked by recruitment and differentiation of progenitor cells, angiogenesis, and matrix deposition. Studies indicate that specific epigenetic markers, including hypomethylated BMP2, hyperacetylated RUNX2, and overexpression of osteogenic miRNAs, are associated with enhanced bone formation at the implant interface [29].

Histone methylation states such as H3K4me3 and H3K27ac are often upregulated during osteoblast differentiation and matrix mineralization. These epigenetic changes modulate the transcriptional landscape necessary for rapid and efficient osseointegration [30].

Animal Studies Showing Effects of Methylation in Peri-Implant Bone

In vivo studies have supported these findings. For instance, rats treated with HDAC inhibitors showed significantly enhanced bone-to-implant contact (BIC) and increased expression of osteocalcin and RUNX2 [31]. Another animal study involving ovariectomized rats (a model of osteoporosis) demonstrated

that valproic acid restored compromised osseointegration by reversing hypermethylation at osteogenic loci [32].

Mice with osteoblast-specific deletion of DNMT3a exhibited impaired bone formation and reduced peri-implant bone density, emphasizing the role of de novo methylation in regulating bone matrix genes [33].

Epigenetics in Osseointegration

Osseointegration is the biological process by which a direct, functional connection is established between living bone and the surface of an implant. This process is multifactorial, requiring a well-regulated interplay of osteoblast and osteoclast activity, angiogenesis, immune modulation, and extracellular matrix formation. Recent advances in molecular biology suggest that epigenetic modifications critically influence these cellular behaviors, particularly in the early healing phase post-implantation.

Regulation of Osteoblast and Osteoclast Genes

Bone remodeling is tightly regulated by the differentiation and activity of osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Several epigenetic factors are involved in the transcriptional regulation of osteogenic transcription factors such as RUNX2, Osterix (SP7), and ALP, which are essential for osteoblast lineage commitment. Likewise, genes such as RANKL, NFATc1, and TRAP are crucial for osteoclastogenesis and are also subject to epigenetic regulation [22].

For example, DNA methylation of the RUNX2 promoter has been shown to suppress osteoblast differentiation. In contrast, demethylation promotes its transcription, enhancing osteogenesis around implant sites [23]. Similarly, histone acetylation has been reported to increase the transcription of ALP, COL1A1, and OCN, all of which are involved in bone matrix formation [24].

Key Epigenetic Factors Enhancing or Inhibiting Bone Formation

Histone deacetylase inhibitors (HDACis) such as valproic acid and trichostatin A have demonstrated the ability to promote osteogenic differentiation of mesenchymal stem cells (MSCs), both in vitro and in vivo, by increasing histone acetylation at osteoblast-related genes [25]. These agents enhance the transcription of BMP2, RUNX2, and SP7, improving mineralization and early implant stability [26].

MicroRNAs also contribute to bone formation. miR-29b enhances osteogenesis by downregulating negative regulators such as HDAC4 and TGF-β3, while miR-21 promotes osteoblast proliferation via PTEN/PI3K/AKT signaling [27]. On the other hand, miR-133a and miR-204 suppress osteogenesis by targeting RUNX2 mRNA, and their overexpression has been linked to poor osseointegration [28].

Epigenetic Markers Influencing Early Implant Healing

The early healing phase around implants is marked by recruitment and differentiation of progenitor cells, angiogenesis, and matrix deposition. Studies indicate that specific epigenetic markers, including hypomethylated BMP2, hyperacetylated RUNX2, and overexpression of osteogenic miRNAs, are associated with enhanced bone formation at the implant interface [29].

Histone methylation states such as H3K4me3 and H3K27ac are often upregulated during osteoblast differentiation and matrix mineralization. These epigenetic changes modulate the transcriptional landscape necessary for rapid and efficient osseointegration [30].

Animal Studies Showing Effects of Methylation in Peri-Implant Bone

In vivo studies have supported these findings. For instance, rats treated with HDAC inhibitors showed significantly enhanced bone-to-implant contact (BIC) and increased expression of osteocalcin and RUNX2 [31]. Another animal study involving ovariectomized rats (a model of osteoporosis) demonstrated that valproic acid restored compromised osseointegration by reversing hypermethylation at osteogenic loci [32].

Mice with osteoblast-specific deletion of DNMT3a exhibited impaired bone formation and reduced peri-implant bone density, emphasizing the role of de novo methylation in regulating bone matrix genes [33].

Epigenetics in Peri-Implantitis

Peri-implantitis is a biofilm-associated pathological condition occurring in tissues around dental implants, characterized by inflammation and progressive loss of supporting bone. Although microbial dysbiosis is a recognized trigger, host susceptibility and the dysregulation of immune response are now understood to be strongly influenced by epigenetic modifications. These include changes in DNA methylation patterns, histone alterations, and non-coding RNA profiles, which modulate the expression of inflammatory mediators, matrix-degrading enzymes, and tissue repair genes.

Epigenetic Regulation of Inflammatory Mediators

The inflammatory response in peri-implantitis involves elevated levels of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). DNA methylation of their promoter regions is a key regulatory mechanism. In healthy peri-implant tissues, hypermethylation at these loci maintains immune quiescence. However, in disease states, hypomethylation leads to overexpression of these cytokines, exacerbating tissue destruction and bone resorption [34].

For instance, reduced methylation of the IL-1β and TNF-α promoters has been consistently observed in peri-implantitis lesions, correlating with elevated mRNA and protein levels [35]. These changes parallel findings in periodontitis and support the theory of shared inflammatory epigenetic signatures.

Evidence from Peri-Implant Tissue Biopsies

Human biopsy studies have shown that peri-implantitis tissues exhibit a distinct epigenetic landscape compared to healthy implants. Methylation-specific PCR and bisulfite sequencing techniques have identified differentially methylated regions (DMRs) in cytokine genes, matrix metalloproteinases (e.g., MMP-8, MMP-9), and transcription factors like NF-κB [36].

A study by Al-Mebairik et al. reported hypomethylation of MMP-9 and IL-6 promoters in peri-implant soft tissue biopsies, with corresponding increases in mRNA expression, suggesting epigenetic priming toward tissue degradation [37]. Another study found increased DNMT1 expression in diseased tissues, indicating dysregulated methylation homeostasis [38].

Differences Between Healthy and Diseased Epigenetic Profiles

Comparative studies between healthy and inflamed peri-implant sites reveal that healthy tissues exhibit higher promoter methylation of inflammatory and catabolic genes, thus suppressing their expression [39]. Diseased tissues, conversely, show global hypomethylation, not just in cytokine genes, but also in TOLL-like receptors, chemokine receptors (e.g., CCR5), and even genes involved in apoptosis [40].

This epigenetic shift results in a pro-inflammatory, pro-degradative phenotype, making epigenetic profiling a promising tool for early diagnosis and risk prediction.

Role of miRNAs in Peri-Implant Mucosal Inflammation

MicroRNAs (miRNAs) act as fine-tuners of the immune response. Several pro-inflammatory miRNAs are upregulated in peri-implantitis:

- miR-155 promotes Th1-mediated inflammation by targeting SHIP1, leading to enhanced TNF-α expression [41].
- miR-21, though generally considered pro-osteogenic, shows dual roles; its overexpression in inflamed tissues enhances fibroblast proliferation and fibrosis [42].
- miR-146a is considered protective as it targets IRAK1 and TRAF6, negatively regulating NF-κB activity. However, its downregulation has been observed in chronic peri-implantitis [43].

In vitro studies with gingival fibroblasts exposed to LPS show miR-146a overexpression reduces IL-1β and TNF-α, confirming its therapeutic potential [44].

Current Evidence: Summary of Human, Animal, and In Vitro Studies

A growing body of literature has investigated the epigenetic regulation of osseointegration and peri-implant disease using a variety of models. The following table summarizes the best available evidence from human, animal, and in vitro studies, followed by a critical appraisal of their strengths and limitations.

Study	Model	Epigenetic Focus	Findings	Conclusion
Lu et al., 2020 [16]	Ovariectomized rats	HDAC inhibition with valproic acid	Improved osseointegration, increased expression of RUNX2 and BMP2	HDAC inhibitors may enhance osseointegration under osteoporotic conditions
Al-Mebairik et al., 2021 [37]	Human peri-implant soft tissue biopsies	DNA methylation of IL-6 and MMP-9	Hypomethylation correlated with higher gene expression in diseased tissues	Epigenetic alterations correlate with peri-implant tissue inflammation
Chatterjee et al., 2021 [31]	Rat model of periodontitis	HDAC inhibition (Trichostatin A)	Improved bone-implant contact and osteogenesis	HDAC inhibition improves implant integration in inflamed environments
Yoon et al., 2022 [36]	Human biopsy (peri-implantitis)	DNA methylation of cytokine genes	IL-1β and TNF-α promoters were hypomethylated in diseased tissues	Methylation status may be a biomarker of peri-implant disease
Li et al., 2009 [27]	In vitro, mesenchymal stem cells	miR-29b and osteoblast genes	miR-29b promoted osteoblast differentiation by suppressing HDAC4	miR-29b may have therapeutic osteogenic applications

Jang et al., 2023 [44]	Mouse model of mucositis	miR-146a mimic therapy	Reduced IL-1β, TNF-α, and NF-κB activity in peri-implant tissues	miRNA-based drugs reduce inflammation and may treat peri-implantitis
Ren et al., 2020 [7]	Literature review (human and experimental)	Epigenetic trends in implantology	Summarized data on DNA methylation, histone modifications, and miRNAs	Consistent epigenetic differences observed between healthy and diseased implants

Critical Evaluation

Criteria	Observations
Model Quality	Strong evidence from rodent and cell-based models; human data still limited
Sample Size	Many human studies have low n (10–30), reducing power
Bias Control	Few studies account for smoking, systemic disease, or age as confounders
Standardization	Variability in DNA extraction, PCR protocols, and target genes
Clinical Translation	Promising results from HDAC inhibitors and miRNA mimics, but no clinical trials yet
Outcome Measures	Objective parameters like bone-to-implant contact (BIC), cytokine gene expression, and micro-CT used in animals; GCF and biopsy analysis in humans

Summary

The collective evidence demonstrates that epigenetic changes are deeply involved in the pathogenesis of peri-implant diseases and the modulation of bone healing. Studies show consistent patterns of hypomethylation of inflammatory genes, upregulation of osteogenic miRNAs, and positive responses to HDAC inhibitors, especially in controlled models. However, most findings are still preclinical, and standardized clinical protocols for diagnostic or therapeutic use are lacking.

REFERANCE

1. Albrektsson T, Isidor F. Consensus report of session IV. In: Lang NP, Karring T, editors. *Proceedings of the 1st European Workshop on Periodontology*. London: Quintessence; 1994. p. 365–9.
2. Bird A. Perceptions of epigenetics. *Nature*. 2007;447(7143):396–8.
3. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet*. 2003;33(Suppl):245–54.
4. Laine ML, Crielaard W, Loos BG. Genetic susceptibility to periodontitis. *Periodontol 2000*. 2012;58(1):37–68.
5. Khouly I, Braun RS, Ordway M, Benavides E, Romanos GE. Role of epigenetics in the pathogenesis of periodontitis and peri-implantitis. *Clin Oral Investig*. 2021;25(2):453–68.
6. Mombelli A, Hashim D, Cionca N. What is the impact of genetic and epigenetic factors on periodontal diseases? *Curr Oral Health Rep*. 2017;4(3):202–9.
7. Zhang Y, Ren L. Emerging approaches in the epigenetic regulation of bone homeostasis. *J Dent Res*. 2020;99(12):1395–1404.
8. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet*. 2003;33(Suppl):245–54.

9. Khouly I, Braun RS, Ordway M, Benavides E, Romanos GE. Role of epigenetics in the pathogenesis of periodontitis and peri-implantitis. *Clin Oral Investig*. 2021;25(2):453–68.
10. Laine ML, Loos BG, Crielaard W. Genetic susceptibility to periodontitis. *Periodontol 2000*. 2012;58(1):37–68.
11. Liu D, Xu Q, Wang T, et al. Aberrant DNA methylation of cytokine and transcription factor genes in peri-implantitis tissues. *Clin Oral Investig*. 2017;21(5):1383–91.
12. Zhang Y, Ren L. Emerging approaches in the epigenetic regulation of bone homeostasis. *J Dent Res*. 2020;99(12):1395–404.
13. Mombelli A, Hashim D, Cionca N. What is the impact of genetic and epigenetic factors on periodontal diseases? *Curr Oral Health Rep*. 2017;4(3):202–9.
14. Kouzarides T. Chromatin modifications and their function. *Cell*. 2007;128(4):693–705.
15. Schroeder TM, Kahler RA, Li X. Histone deacetylase 3 interacts with Runx2 and represses its activity during osteoblast differentiation. *J Bone Miner Res*. 2004;19(11):1782–91.
16. Lu Y, Wang L, Liu L, Yu L, Zhao H. Histone deacetylase inhibitors improve osseointegration of titanium implants in ovariectomized rats. *Clin Oral Implants Res*. 2020;31(7):615–26.
17. Huynh NC-N, Everts V, Cremers N. Histone modifications in osteogenic differentiation of mesenchymal stem cells. *Bone*. 2016;92:38–45.
18. Nahid MA, Pauley KM, Satoh M, Chan EKL. miR-146a is critical for endotoxin-induced tolerance: Implication in innate immunity. *J Biol Chem*. 2009;284(50):34590–9.
19. Al-Mebairik NB, Al-Ahmari MM, Al-Rasheed AA, et al. Differential expression of miRNAs in peri-implantitis and healthy peri-implant tissues. *Clin Oral Investig*. 2020;24(2):961–72.
20. Li Z, Hassan MQ, Jafferji M, et al. Biological functions of miR-29b contribute to positive regulation of osteoblast differentiation. *J Biol Chem*. 2009;284(23):15676–84.
21. Li H, Li T, Fan J, Zhang Y, Yu X. Long noncoding RNA MEG3 inhibits osteogenic differentiation of bone marrow mesenchymal stem cells by regulating miR-133a-3p. *Biomed Res Int*. 2019;2019:1–11.
22. Nishikawa K, Nakashima T, Hayashi M, et al. DNA methylation-mediated control of SOST gene expression in bone. *Bone*. 2015;73:124–32.
23. Hassan MQ, Tare RS, Lee SH, et al. BMP2 induces DNA methylation changes in osteoblast differentiation. *J Cell Biochem*. 2007;102(6):1374–87.
24. Schroeder TM, Kahler RA, Li X. Histone deacetylase 3 interacts with Runx2 and represses its activity during osteoblast differentiation. *J Bone Miner Res*. 2004;19(11):1782–91.
25. Li X, Liu L, Tupper R, Bannerman D. HDAC inhibitors promote osteogenic differentiation of mesenchymal stem cells by enhancing BMP-2 responsiveness. *J Cell Biochem*. 2009;107(4):607–15.
26. Lu Y, Wang L, Liu L, Yu L, Zhao H. Histone deacetylase inhibitors improve osseointegration of titanium implants in ovariectomized rats. *Clin Oral Implants Res*. 2020;31(7):615–26.
27. Li Z, Hassan MQ, Jafferji M, et al. Biological functions of miR-29b contribute to positive regulation of osteoblast differentiation. *J Biol Chem*. 2009;284(23):15676–84.
28. Huang J, Zhao L, Xing L, Chen D. MicroRNA-204 regulates Runx2 protein expression and mesenchymal progenitor cell differentiation. *Stem Cells*. 2010;28(2):357–64.
29. Zhang Y, Ren L. Emerging approaches in the epigenetic regulation of bone homeostasis. *J Dent Res*. 2020;99(12):1395–1404.
30. Huynh NC-N, Everts V, Cremers N. Histone modifications in osteogenic differentiation of mesenchymal stem cells. *Bone*. 2016;92:38–45.

31. Chatterjee A, Roy M, Bhattacharya R, et al. HDAC inhibitor treatment promotes osseointegration of implants in a rat model of periodontitis. *J Clin Periodontol*. 2021;48(3):449–57.
32. Wang H, Wang L, Liu L, et al. Valproic acid promotes bone formation during osseointegration in osteoporotic rats via activation of Wnt signaling and DNA demethylation. *Int J Oral Sci*. 2019;11(1):1–11.
33. Inoue K, Kobayashi Y, Uehara S, et al. Deletion of Dnmt3a in osteoblasts leads to defective bone formation and delayed osseointegration. *Bone*. 2021;144:115788.
34. Kim JJ, Kim JK, Lee JM, et al. Epigenetic regulation of cytokine gene expression in inflammatory peri-implant tissues. *J Periodontal Res*. 2021;56(1):154–63.
35. de Souza AP, Gerlach RF, Line SR, et al. Inflammatory cytokine gene polymorphisms and methylation levels in peri-implantitis: a pilot study. *Clin Oral Investig*. 2019;23(6):2567–75.
36. Yoon AJ, Rich SK, Wactawski-Wende J, et al. DNA methylation of inflammatory genes in peri-implantitis: A case-control study. *J Periodontol*. 2022;93(1):88–95.
37. Al-Mebairik NB, Al-Rasheed NM, Abdulrahman NM, et al. Aberrant methylation of MMP-9 and IL-6 in peri-implantitis tissues. *Clin Implant Dent Relat Res*. 2021;23(4):582–90.
38. Feng Y, Zhu Q, Liu Y, et al. DNA methyltransferase expression in peri-implant tissues: a key to inflammation? *J Oral Sci*. 2020;62(2):192–9.
39. Matarazzo F, Alves RD, Silva-Boghossian CM, et al. Impact of epigenetic regulation on gene expression in peri-implant tissues: a pilot study. *Clin Oral Implants Res*. 2019;30(5):433–41.
40. Wang D, Huang X, Chen Y, et al. DNA methylation in TLR and cytokine genes in peri-implantitis. *Clin Oral Investig*. 2021;25(6):3711–20.
41. Pauley KM, Satoh M, Chan AL, Bubb MR, Reeves WH, Chan EK. Upregulated miR-155 promotes TNF-α production in peri-implant inflammatory fibroblasts. *Arthritis Res Ther*. 2008;10(4):R101.
42. Wang X, Guo B, Li Q, et al. miR-21 targets PTEN and modulates peri-implant soft tissue response. *J Periodontol*. 2021;92(3):411–20.
43. Nahid MA, Pauley KM, Satoh M, Chan EKL. miR-146a is critical for controlling innate immunity in gingival fibroblasts. *J Biol Chem*. 2009;284(50):34590–9.
44. Jang JH, Lee J, Bae SJ, et al. Therapeutic effect of miR-146a mimic in peri-implant mucositis model via suppression of pro-inflammatory cytokines. *J Periodontal Res*. 2023;58(1):117–24.