Biomaterials 324 (2026) 123491

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

# Soft tissue integration around dental implants: A pressing priority

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ARTICLE INFO

*Keywords:*
Soft tissue sealing
Dental implant
Abutment
Peri-implantitis
Surface modification
Tissue regeneration

ABSTRACT

While osseointegration has traditionally been the focal point of dental implant design, recent research highlights the equally crucial role of establishing a resilient and biologically integrated soft tissue seal for long-term implant success. This review critically examines recent advances (primarily from the past five years) that elucidate the molecular, cellular, and materials science strategies essential for enhancing peri-implant soft tissue integration. Key factors include precisely engineered surface topographies at micro- and nanoscale levels, surface chemical modifications that enhance wettability and protein adsorption, and biomimetic coatings incorporating extracellular matrix-derived peptides, chemokines, and growth factors. Recent studies underscore the impact of laser micro- and nano-texturing, plasma treatments, and biofunctionalization in modulating fibroblast and epithelial cell behaviors, accelerating tissue attachment, and mitigating early inflammatory responses. Emerging implant-abutment designs, such as platform switching and transmucosal zirconia abutments, demonstrate improved soft tissue stability and reduce crestal bone loss. Additionally, the immunomodulatory potential of next-generation materials offers promising avenues for directing macrophage polarization and enhancing wound resolution. Collectively, this review synthesizes the latest evidence on material-driven and biological strategies for engineering a stable soft tissue interface. It provides a translational roadmap for the development of implant systems optimized for long-term soft tissue health, addressing a critical unmet need in dental implantology.

## 1. Introduction

Dental implants are a cornerstone of modern restorative dentistry, providing patients with a durable, functional, and aesthetically pleasing solution for tooth loss. Their long-term success is governed by two critical biological processes: osseointegration and soft tissue integration (STI). Osseointegration refers to the direct structural and functional connection between living bone and the surface of a load-bearing implant, a concept first introduced by Brånemark [1]. This bone-implant interface is essential for mechanical stability and implant longevity.

Equally critical, though often underemphasized, is STI, which involves the stable attachment of peri-implant mucosa to the implant abutment. While soft tissue integration does not directly govern osseointegration, it plays a critical supportive role by forming a biological seal that protects the underlying bone-implant interface from microbial invasion and inflammatory insult, thereby contributing to the long-term stability of osseointegration. A significant clinical consequence of insufficient STI is peri-implantitis, a progressive inflammatory condition marked by soft tissue inflammation and alveolar bone loss around a functioning implant. Notably, peri-implantitis is often preceded by peri-implant mucositis, a reversible inflammatory condition confined to the soft tissues [2]. If left untreated, mucositis can advance to peri-implantitis, ultimately leading to implant failure. Peri-implant mucositis is highly prevalent, affecting up to 80 % of implant patients, while peri-implantitis impacts approximately 28–56 % of implants, depending on population demographics and diagnostic criteria [3–5].

Despite the pivotal role of STI in the long-term success of dental implants, research and clinical innovation have historically prioritized osseointegration. As a result, a significant knowledge gap remains regarding the biological and immunological mechanisms that govern soft tissue responses to implant materials. Successful STI requires a multifaceted approach that incorporates not only material and surface engineering but also a deep understanding of the peri-implant immune microenvironment.

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https://doi.org/10.1016/j.biomaterials.2025.123491
Received 13 February 2025; Received in revised form 1 June 2025; Accepted 8 June 2025
Available online 9 June 2025

This review critically evaluates dental implant materials through the lens of their influence on peri-implant soft tissue healing, immune modulation, and barrier function. It explores emerging strategies aimed at achieving stable and durable STI, including nanostructured topographies, bio-inspired surface coatings, and biomolecular functionalization. Special attention is given to approaches that modulate local immune responses to promote pro-regenerative healing while minimizing chronic inflammation and fibrotic encapsulation. Additionally, the incorporation of antimicrobial features is discussed to preserve tissue health and seal integrity. By addressing both biological and material-based strategies and emphasizing the importance of immune-tissue-material interactions, this review aims to guide future research and clinical practices toward minimizing soft tissue complications.

## 2. Biological and physical aspects of oral soft tissue healing and integration

The integration of soft tissue around dental implants is governed by a complex interplay of biological processes and material-related physical cues. Unlike osseointegration, which has been extensively studied, STI remains less understood despite its critical role in preventing peri-implant infections and ensuring long-term implant stability. This section outlines the biological cascade that governs peri-implant soft tissue healing, draws key distinctions between healing around natural teeth and implants, and explores how material properties influence tissue behavior at the implant interface.

### *2.1. Phases of peri-implant soft tissue healing: a distinct biological cascade*

Soft tissue healing around dental implants, though sharing fundamental mechanisms with general wound healing, exhibits unique features due to the distinct anatomy and physiology of the oral mucosa, the absence of the periodontal ligament (PDL), and the presence of a foreign material interface [6]. The peri-implant mucosa comprises a junctional epithelium and an underlying connective tissue zone that together form a biological seal essential for protecting the peri-implant bone from microbial invasion. Within this complex structure, the epithelium plays a crucial role by forming a physical and immunological barrier through keratinocyte proliferation, differentiation, and hemidesmosome formation, which secure attachment to the implant surface. Concurrently, the connective tissue supports this barrier by providing mechanical strength, producing extracellular matrix (ECM) components, and modulating the immune response [7–9]. Healing in this challenging environment is continuously influenced by factors such as salivary flow, masticatory stress, and persistent microbial exposure, all of which shape the dynamics of soft tissue integration [10]. Soft tissue healing process is broadly categorized into five overlapping and continuous phases, each involving tightly regulated cellular and molecular events (Fig. 1).

#### *2.1.1. Step 1: hemostasis (0–6 h post-surgery)*

The healing process around dental implants begins immediately after surgical placement with the hemostasis phase. Vascular injury causes vasoconstriction and platelet activation, leading to the formation of a fibrin-rich clot that not only prevents bleeding but also provides a temporary matrix for incoming cells. This clot is enriched with growth factors such as platelet-derived growth factor and transforming growth factor-beta, which initiate cellular recruitment and migration [11]. Early activation of keratinocytes also occurs during this phase, laying the groundwork for epithelial wound coverage [12].

#### *2.1.2. Step 2: inflammation (6 h–3 days)*

The inflammatory phase follows hemostasis and is characterized by the infiltration of neutrophils and monocytes. Neutrophils are the first to arrive, playing a role in microbial clearance, followed by macrophages which coordinate the transition to tissue regeneration [12]. In peri-implant soft tissues, keratinocytes play a crucial immunomodulatory role beyond simply forming a barrier. These cells produce cytokines such as interleukin-1β and tumor necrosis factor-alpha, and antimicrobial peptides like β-defensins, which contribute to the innate immune defense. The activity of keratinocytes during this stage not only helps regulate inflammation but also prepares the wound for re-epithelialization [6].

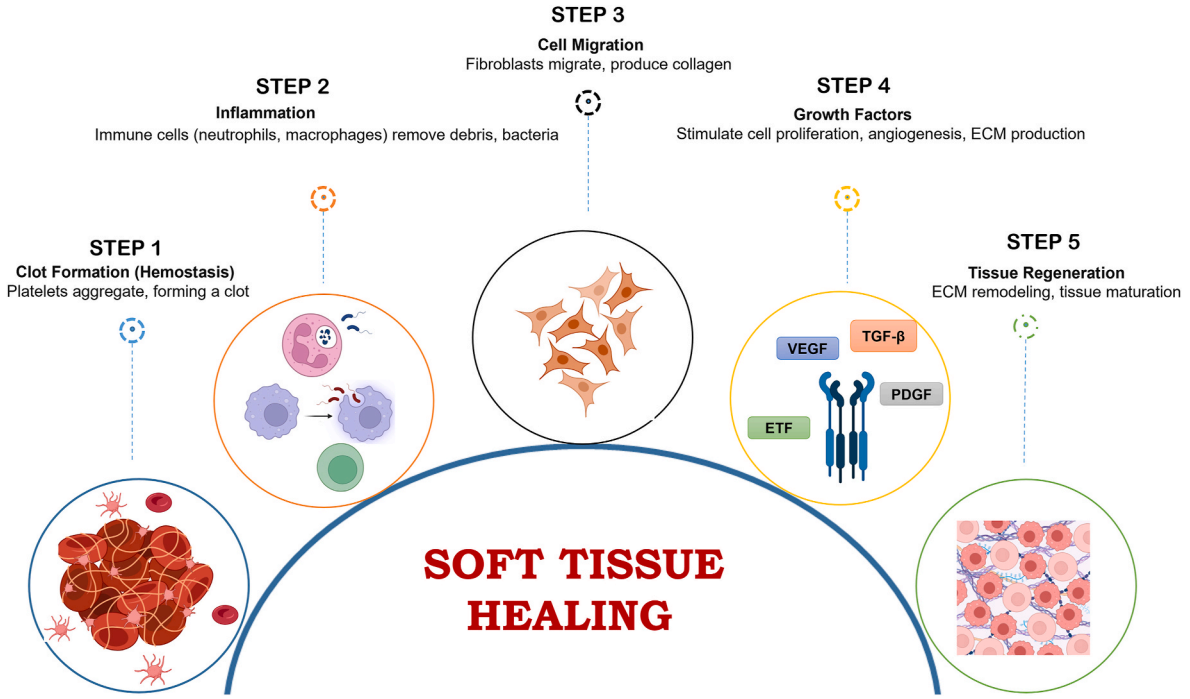


**Fig. 1.** Biological stages of peri-implant soft tissue healing.

#### 2.1.3. Step 3: proliferation phase – part I: re-epithelialization and granulation (2–7 days)

During proliferation, basal keratinocytes migrate and proliferate to restore epithelial coverage over the implant site. Their differentiation into a keratinized epithelium is critical, as the keratinized layer acts as a physical and immunological barrier, providing resistance against mechanical stress (the physical forces generated from mastication, oral hygiene procedures, and micromotion at the implant-abutment interface that can affect the soft tissue seal) and microbial invasion [13–16]. Hemidesmosome formation anchors keratinocytes to the implant surface but is limited to the apical peri-implant epithelium [17]. This contrasts with natural teeth, where hemidesmosomes are more widely distributed along the junctional epithelium, offering a stronger and more protective seal. Keratinocytes also contribute to immune defense by producing antimicrobial peptides and signaling molecules essential for barrier function [8,17].

#### 2.1.4. Step 4: proliferation phase – part II: connective tissue formation and angiogenesis (7–21 days)

At this phase, gingival fibroblasts deposit ECM proteins to rebuild the connective tissue beneath the epithelium, while angiogenesis restores blood supply critical for healing [18].

#### 2.1.5. Step 5: maturation and remodeling (3 weeks to several months)

In the final phase, the epithelium continues to stratify and mature. Keratinocyte differentiation progresses toward the formation of a keratinized epithelial layer, which is critical for ensuring a durable and resilient soft tissue seal. This keratinized layer provides both mechanical resistance and immune protection, acting as a physical and immunological barrier against microbial penetration [19]. The connective tissue undergoes remodeling, with fibroblasts realigning collagen fibers and enhancing tissue stability [12]. The reduced vascularity and cellularity observed in the remodeled tissue marks the completion of the healing process.

### 2.2. Soft tissue healing around natural teeth vs dental implants

Soft tissue healing is essential for the long-term stability of natural teeth and dental implants, yet the underlying anatomical and biological differences between the two result in distinct healing dynamics. In natural dentition, the presence of the PDL, cementum, and alveolar bone forms a strong connective tissue framework. Sharpey's fibers insert perpendicularly into the cementum and alveolar bone, contributing to a resilient and functional attachment apparatus (Fig. 2). This architecture supports a well-vascularized and immunocompetent environment that favors rapid and effective healing. Keratinocytes are essential for re-establishing the epithelial barrier during wound healing. They migrate to the wound site, proliferate, and undergo differentiation to restore a stratified epithelium. The resulting keratinized layer contributes to mechanical resilience and helps limit microbial penetration [20]. Additionally, the re-formation of cell–matrix adhesion structures, such as hemidesmosomes, plays a crucial role in re-establishing stable attachment of basal keratinocytes to the underlying basement membrane [21,22].

In contrast, dental implants lack both the PDL and cementum, resulting in a fundamentally different soft tissue interface (Fig. 2). Connective tissue fibers align parallel or circularly around the implant without inserting into its surface, leading to a weaker mechanical seal.

The epithelial barrier, though formed via hemidesmosome adhesion to the implant surface, is less stable and more susceptible to disruption. Compounding this is the reduced vascular supply in the peri-implant mucosa, which relies primarily on supraperiosteal and marrow-derived vessels. This limited vascularity delays healing and impairs the local immune response. Consequently, the peri-implant mucosa forms a biologic seal rather than a true connective tissue attachment, rendering it more vulnerable to microbial ingress and mechanical trauma [8]. Moreover, the foreign body nature of implants promotes a persistent low-grade inflammatory state. The compromised immune surveillance—due to fewer resident immune cells and diminished vascular support—means that even minimal plaque accumulation can trigger an exaggerated and rapidly progressing inflammatory response [23,24]. Unlike periodontitis around teeth, which tends to progress gradually and can often be managed conservatively, peri-implantitis develops more aggressively and may necessitate surgical intervention or implant removal [25].

### 2.3. Physical factors-material properties

The success of STI is closely influenced by the physicochemical properties of the implant surface, which govern early biological responses such as protein adsorption, cellular adhesion, inflammatory signaling, and matrix remodeling. Among these surface characteristics, wettability, topography, chemistry, charge, and immunomodulatory potential have emerged as key parameters.

Surface wettability is a fundamental factor influencing STI around dental implants. It enhances early biological events such as protein adsorption, cellular adhesion, and spreading, all of which are essential for establishing a stable peri-implant mucosal seal [26]. Improved

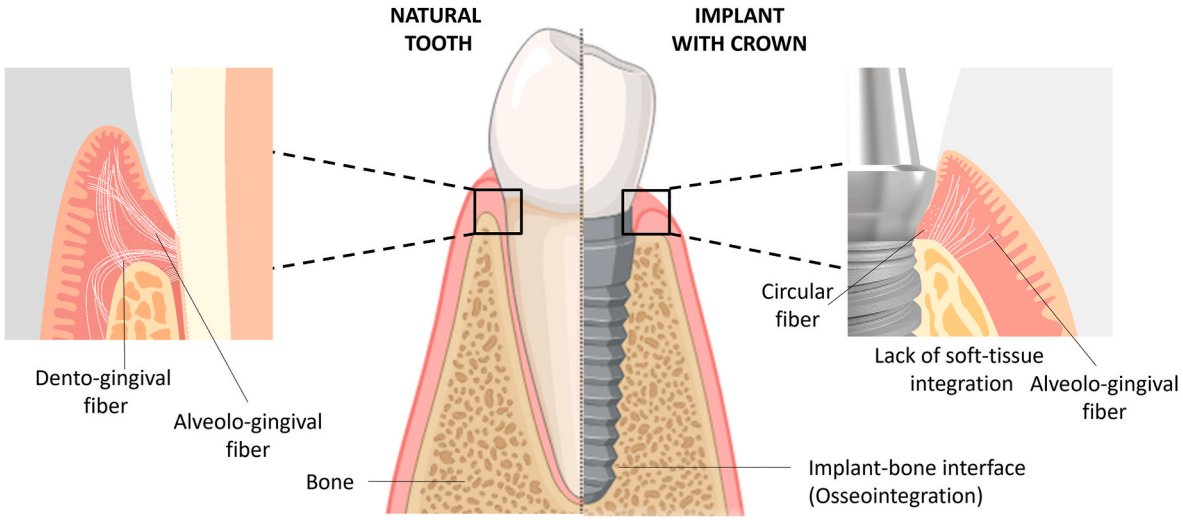


**Fig. 2.** Differences in the STI between natural tooth and dental implant.

wettability, often achieved through hydrophilic surface treatments, has been shown to promote epithelial and fibroblast attachment, supporting better clinical outcomes. This property is largely governed by surface energy, which affects the contact angle of liquids as described by Young's equation—a key principle for predicting and optimizing implant–tissue interactions [27].

Closely related to wettability is surface topography, which influences STI by providing structural cues for cellular behavior. Surfaces engineered with hierarchical micro- and nano-scale features not only increase available surface area for protein adsorption but also enhance cellular orientation, adhesion, and ECM deposition. Nanostructures such as nanotubes and nano-spikes can guide fibroblast alignment, encourage organized ECM formation, and reduce epithelial downgrading, contributing to a more effective tissue seal [28,29].

Importantly, the combination of micro- and nano-topographies in a biomimetic design has gained prominence for promoting eukaryotic cell adhesion while discouraging bacterial colonization. For example, in vitro studies have shown that grooved or moderately rough surfaces upregulate key adhesion genes (e.g., FAK, α-SMA, integrins), thereby strengthening connective tissue interactions [30,31]. However, excessive smoothness (Ra <0.2 μm) may impair epithelial sealing, while excessive roughness can increase bacterial adhesion [32,33]. These findings underscore the importance of precisely tuned surface roughness to achieve a balance between STI and microbial defense.

Surface chemistry also plays a critical role, particularly in modulating host responses under bacterial challenge. One in vitro model using a transwell system with human keratinocytes cultured above gingival fibroblasts demonstrated that hydrophilic surfaces provided superior barrier function and fibroblast integration compared to hydrophobic silicone substrates [34]. This result emphasized the importance of combining surface chemistry and wettability in supporting peri-implant tissue stability.

Beyond cell adhesion, surface-induced blood interactions significantly shape STI. Rough and hydrophilic titanium surfaces accelerate coagulation and support dense fibrin clot formation, which not only facilitates fibroblast anchorage but also promotes an anti-inflammatory, M2-type macrophage phenotype conducive to healing [35,36]. Conversely, smoother surfaces may favor keratinocyte attachment in the absence of blood, yet they are often linked to a more pro-inflammatory (M1) cytokine profile [36,37]. This dichotomy highlights the need for tailored surface designs based on the desired tissue response.

Differential cellular responses further complicate implant surface design. Human gingival fibroblasts (HGFs) generally favor minimally rough to rough surfaces for proliferation, whereas keratinocytes perform better on smoother substrates. Cytotoxicity patterns also differ: keratinocytes show higher stress responses on smooth surfaces, while fibroblasts are more sensitive to intermediate roughness [38]. These cell-type-specific behaviors demand nuanced topographical optimization for effective epithelial and connective tissue integration.

Increasing attention has also turned to the immunomodulatory landscape of STI. A balanced macrophage response is essential: while M1 macrophages initiate defense and inflammation via cytokines like IL-1β and TNF-α, M2 macrophages support tissue remodeling and healing via IL-10, IL-13, and TGF-β [39,40]. Hydrophilic and bioactive surfaces have been shown to promote M2 polarization, aligning with more favorable healing outcomes. This suggests that wettability, beyond influencing cell adhesion, also plays a key role in immune modulation.

Another emerging parameter is surface charge. It modulates protein adsorption and cell attachment by influencing electrostatic interactions. Fibroblast adhesion is improved on positively charged surfaces due to stronger electrostatic attraction, which enhances cell attachment and spreading [41]. In contrast, negatively charged surfaces can bind calcium ions ($Ca^{2+}$), which then interact with phosphate to form bioactive apatite layers critical for mineralization and implant stability. In addition to facilitating mineral formation, calcium ions play an important role in regulating fibroblast migration, proliferation, and cellular signaling, all of which promote successful STI. Therefore, both positively and negatively charged surfaces support fibroblast function through distinct but complementary pathways [42,43].

In summary, while surface wettability exerts a dominant influence on soft tissue behavior, it works in concert with topography, charge, and immunomodulation to determine clinical outcomes. Rather than isolating a single factor, a synergistic design approach—combining appropriate surface chemistry, nano/microstructuring, charge, and immunomodulatory cues—is crucial for optimizing peri-implant soft tissue integration.

## 3. Dental implant materials

Dental implants typically consist of three key components: the fixture, abutment, and crown. The fixture is the root-form element surgically placed into the alveolar bone, serving as the foundation for osseointegration. The abutment is the intermediate component that connects the fixture to the prosthetic crown, traversing the soft tissue interface. Together, the abutment and the crown define the transmucosal region of the implant system, which plays a pivotal role in STI. This region is directly exposed to the oral environment and is crucial in establishing a stable biological seal that protects the underlying bone from microbial and inflammatory insults [44]. As such, the surface properties and design of both the abutment and crown have a significant influence on the quality of the peri-implant mucosal attachment and the long-term success of dental implants.

### 3.1. Titanium and its alloys

Commercially pure titanium (CP Ti), particularly Grades III and IV, remains the gold standard for dental implants due to its proven biocompatibility, corrosion resistance, and mechanical integrity [45]. Grade IV CP Ti, with its superior tensile strength (~550–650 MPa) compared to lower grades, supports load-bearing applications without compromising biocompatibility [46]. The spontaneous formation of a stable $TiO_2$ passive oxide film on titanium surfaces plays a pivotal role in modulating the peri-implant soft tissue response by reducing inflammatory cytokine release and promoting epithelial cell adhesion [47].

Titanium alloys such as Ti–6Al–4V and Ti–6Al–7Nb are widely used for implant bodies and abutments due to their superior mechanical properties, and corrosion resistance [48]. However, studies report differential cellular responses attributed to alloying elements: aluminum and vanadium ions released in Ti–6Al–4V can induce cytotoxicity and impair fibroblast proliferation in vitro [49], potentially compromising epithelial barrier integrity. Conversely, Ti–6Al–7Nb, which replaces vanadium with niobium, exhibits reduced ion cytotoxicity and improved biocompatibility [50]. Importantly, implant surface modifications, such as anodization, acid etching, and sandblasting, influence surface roughness and wettability, which have been shown to promote soft tissue cell adhesion and reduce peri-implant inflammation more effectively than bulk alloy composition alone [33,51]. Yet, the majority of studies focus on osseointegration endpoints; specific mechanistic insights into soft tissue cell interaction with titanium surfaces remain limited, underscoring the need for STI-focused material engineering.

### 3.2. Titanium-zirconium alloys

Titanium-zirconium (Ti–Zr) alloys, such as Roxolid® (about 13–17 % Zr), have emerged as promising alternatives, combining the strength benefits of titanium alloys with enhanced biocompatibility [52]. Ti–Zr alloys exhibit a modulus of elasticity (~80 GPa) closer to natural bone than Ti–6Al–4V (~110 GPa), potentially reducing stress shielding and improving biomechanical compatibility with soft tissues [53].

Recent in vitro studies indicate that Ti–Zr surfaces significantly enhance HGFs proliferation and attachment compared to CP titanium [54]. Additionally, Ti–Zr surfaces downregulate pro-inflammatory

cytokines such as IL-6 and TNF-α, suggesting a more favorable immunomodulatory profile that supports stable peri-implant mucosal sealing.

### 3.3. Zirconia-based ceramics

Yttria-stabilized tetragonal zirconia polycrystals (Y-TZP) are increasingly adopted for esthetic abutments and implant bodies, especially where metal-free solutions are desired [55]. Zirconia offers superior fracture toughness (9–10 MPa $m^{1/2}$) and resistance to plaque accumulation, which contributes to reduced peri-implant mucositis and inflammation compared to titanium [56–58].

Keratinocyte and fibroblast cultures show enhanced adhesion and spreading on polished zirconia surfaces, with lower expression of inflammatory markers (IL-1β, IL-8) relative to titanium. Moreover, zirconia's ceramic oxide nature eliminates concerns related to metal ion release, a known trigger of hypersensitivity reactions that can compromise STI [59]. Zirconia offers high fracture toughness for a ceramic and superior aesthetics, but it remains more brittle than titanium alloys and is susceptible to aging effects that may compromise long-term durability. Clinically, titanium alloys are often favored in high-stress situations, while zirconia implants are primarily chosen as an esthetic alternative in low-to moderate-load zones [60].

### 3.4. Cobalt-chromium alloys

Cobalt-chromium-molybdenum (Co–Cr–Mo) alloys, traditionally valued for their hardness and wear resistance in prosthodontics and abutments, have seen limited application in permanent implant fixtures due to unfavorable soft tissue responses. Co–Cr surfaces typically exhibit increased stiffness (~230 GPa) and density compared to titanium alloys, which can exacerbate stress concentrations at the soft tissue interface and promote micro-movements detrimental to STI [61].

Cell culture studies have shown that Co–Cr surfaces significantly reduce HGFs adhesion and proliferation while increasing the secretion of inflammatory mediators such as IL-6 and matrix metalloproteinases (MMPs), which may compromise mucosal barrier integrity. Additionally, the potential release of Co and Cr ions raises concerns about biocompatibility and the risk of allergic reactions [62,63].

### 3.5. Stainless steel and nickel-titanium (nitinol)

Stainless steel (AISI 316L) and nickel-titanium shape-memory alloys (Nitinol) have limited use in permanent dental implants due to their susceptibility to corrosion and ion release issues. Notably, nickel ions are potent allergens and cytotoxins that can trigger chronic inflammation in peri-implant soft tissues [33,64,65]. While Nitinol's superelasticity is advantageous for orthodontic and temporary devices, its use in soft tissue-contacting permanent implants remains contraindicated.

### 3.6. Polymeric materials

Polyether ether ketone (PEEK) is increasingly recognized as a promising metal-free implant abutment material, valued for its bone-like mechanical properties (~3–4 GPa modulus) and radiolucency, which enhance imaging and stress distribution [66]. Unlike natural bone, which undergoes continuous remodeling and dynamic interactions with surrounding tissues, synthetic implant materials rely heavily on their intrinsic and engineered surface properties to mediate biological responses. Native PEEK, for instance, is bioinert and exhibits limited protein adsorption and poor adhesion of soft tissue cells. To address these limitations, surface functionalization strategies—such as plasma treatment, sulfonation, and coatings with bioactive agents like Arg-Gly-Asp (RGD) peptides or hydroxyapatite (HA) nanoparticles—have been developed. These approaches have significantly improved keratinocyte and fibroblast attachment in vitro [35,67], although long-term clinical validation of their effectiveness in enhancing STI remains ongoing.

While the materials listed in Table 1 do not mimic the mechanical properties of bone, their structural stability, surface chemistry, and biocompatibility are critical determinants of STI. The key surface attributes and their biological implications are highlighted to inform the design of next-generation implant interfaces optimized for soft tissue sealing and integration.

Evaluating soft tissue attachment to biomaterials requires a combination of in vitro and in vivo experimental strategies that capture both cellular responses and tissue-level integration. At the cellular level, assays such as cell adhesion, proliferation (e.g., MTT, CCK-8), and gene/protein expression (e.g., *COL1A1*, *E-cadherin*, *FN1*) provide valuable insights into how epithelial cells and fibroblasts interact with different implant surfaces [70]. Immunofluorescence microscopy is frequently employed to visualize focal adhesions (e.g., vinculin, FAK) and tight junctions (e.g., ZO-1), offering a deeper understanding of barrier-forming potential [71]. At the tissue level, histological analysis in animal models remains the gold standard for assessing epithelial attachment length, collagen fiber orientation, and connective tissue contact. Immunohistochemistry further allows for the localization of key proteins such as collagen, cytokeratins, and inflammatory markers [47]. Additionally, mechanical detachment tests and barrier function assays, such as transepithelial electrical resistance or dye permeability, help evaluate the functional integrity of soft tissue attachment. Together, these methods provide a comprehensive evaluation of STI and are essential for screening and optimizing biomaterial surfaces. However, current evaluation approaches still face limitations, which are further discussed in the concluding section on future research directions.

## 4. Surface modification of dental implants

Long-term success of dental implants depends on the establishment of a stable soft tissue seal around the abutment. However, commonly used materials are inherently bioinert and lack the surface features or biochemical signals necessary for effective soft tissue attachment. This deficiency compromises the formation of a tight epithelial and connective tissue interface, increasing the risk of bacterial infiltration, inflammation, and eventual implant failure. To address these challenges, various surface modification techniques are employed to enhance STI. These surface modification techniques can generally be categorized into physical and chemical modifications. Physical modification involves altering the surface topography of the implant, while chemical modification entails applying a layer of new materials or composites to its surface (surface coating). These modifications are designed to promote epithelial adhesion, guide collagen fiber orientation, and modulate immune responses, fostering the development of a functional mucosal barrier that mimics natural tissue attachment around teeth.

### 4.1. Physical modification

Physical surface modification techniques play a pivotal role in modulating the interface between dental implants and surrounding soft tissues. Micro- and nano-scale surface topographies can profoundly influence protein adsorption, cell adhesion, and subsequent tissue integration by mimicking the hierarchical structure of native ECM. Strategies, such as sandblasting, acid etching, anodization, and laser-based patterning, are commonly employed to generate controlled surface roughness, thereby enhancing epithelial and fibroblast responses. This section explores the most recent advancements in micro- and nano-engineered surfaces designed to improve peri-implant soft tissue attachment and reduce early microbial colonization.

#### 4.1.1. Micro-surface features

Micro-scale features primarily influence cell orientation and migration, while nano-textured surfaces mimic the natural ECM at a molecular

**Table 1**
Summary of materials and their implications for STI.

| Material | Specific Type | Elastic Modulus (GPa) | Key Properties | Implications for STI | Ref |
|---|---|---|---|---|---|
| Cortical bone | Human (reference) | ~10–30 | Natural reference for biomechanical compatibility | Ideal baseline for implant biomaterials | [68] |
| Commercially Pure Titanium (CP Ti) | Grades III, IV | ~105–110 | Biocompatible, corrosion-resistant, passive $TiO_2$ layer | Supports fibroblast and epithelial adhesion; standard material | [69] |
| Titanium Alloys | Ti–6Al–4V, Ti–6Al–7Nb | ~110–120 | Enhanced strength; alloy ion release concerns | Alloying elements may impair STI; surface modifications critical | [48, 50] |
| Titanium–Zirconium Alloys | Roxolid® (Ti–Zr ~13–17 %) | ~95–100 | Improved strength; lower modulus; immunomodulatory | Emerging evidence for enhanced fibroblast proliferation and reduced inflammation | [52] |
| Zirconia Ceramics | Y-TZP | ~200 | Esthetic, plaque-resistant, fracture tough | Promotes keratinocyte/fibroblast adhesion; low inflammatory profile | [57] |
| Cobalt–Chromium Alloys | Co–Cr–Mo | ~220–230 | High strength, wear resistance | Reduced fibroblast adhesion; higher inflammation; limited STI | [63] |
| Stainless Steel | AISI 316L | ~190–210 | Economical, corrosion-prone | Limited permanent use; corrosion and ion release impair STI | [33] |
| Nickel–Titanium (Nitinol) | Ni ~55 %, Ti ~45 % | ~40–75 (anisotropic) | Shape-memory, superplastic | Nickel ion release causes hypersensitivity and inflammation | [64, 65] |
| Polyether Ether Ketone (PEEK) | Unmodified and modified | ~3–4 | Bioinert; modifiable surface; bone-like modulus | Requires surface modification for enhanced soft tissue attachment | [67] |

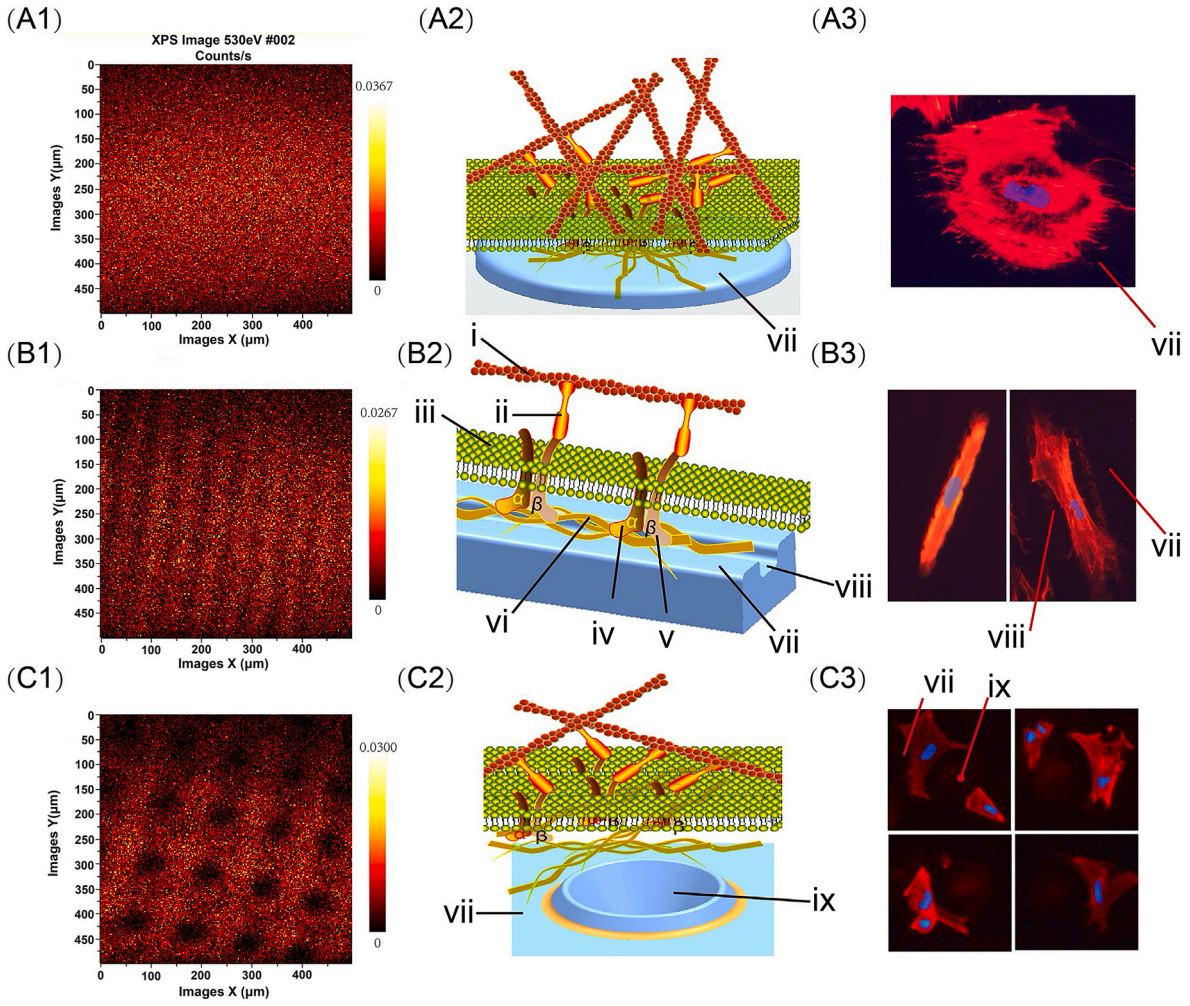


**Fig. 3.** Surface morphology, cell adhesion, and cytoskeletal organization on titanium alloy surfaces modified by different techniques. (A1–C1) SEM images showing the surface topography of titanium alloys treated by (A1) grinding, (B1) sandblasting and acid etching, and (C1) nanosecond laser processing. (A2–C2) Schematic illustrations depicting the interaction between cells and the differently modified titanium surfaces, highlighting changes in surface morphology and cell adhesion behavior. (A3–C3) Fluorescence microscopy images of cytoskeletal organization in cells cultured on the corresponding surfaces, revealing enhanced cell spreading and cytoskeletal arrangement on laser-modified surfaces. Reprinted with permission from Ref. [75]. Copyright 2020, Elsevier.

level, offering intricate topographies that interact directly with cell membranes, adhesion proteins, and signaling pathways.

Among these approaches, laser-based surface structuring emerges as one of the most refined and reproducible techniques. Ultrafast lasers, such as femtosecond and picosecond systems, enables high-precision ablation with minimal thermal damage, allowing the generation of microgrooves, ridges, and hierarchical features [72]. These textures facilitate faster epithelial coverage, increase cytokeratin-19 expression, and reduce inflammatory cytokines such as IL-1β, IL-6, and TNF-α, indicating both structural and immunological benefits [73,74].

In the study by Wang et al., evaluated how mechanical grinding, SLA, and laser texturing affect Ti-6Al-4V titanium surfaces and their influence on osteoblast behavior (Fig. 3). Laser-treated surfaces showed distinct micro/nano structures and highest hydrophilicity, which enhanced osteoblast proliferation and cytoskeletal organization compared to other groups [75]. These findings suggest that nanosecond laser modification enhances surface properties in ways that could significantly improve soft tissue integration, promoting better attachment and healing of the peri-implant mucosa alongside bone regeneration, as evident from other studies.

Similarly, direct metal laser sintering techniques have been employed to fabricate porous titanium architectures that support fibrovascular tissue ingrowth and improve mechanical interlocking between soft tissues and implants. These porous features facilitate nutrient exchange and cellular infiltration, contributing to a more stable peri-implant mucosal environment over time [76].

In parallel, atmospheric pressure plasma (APP) treatment has emerged as another effective surface modification method. Plasma treatment alters surface energy and increases hydrophilicity, thereby enhancing protein adsorption and initial cell attachment. A randomized controlled clinical trial involving 24 patients evaluated the peri-implant mucosal response to APP-treated, Er:YAG laser-treated, and untreated abutments. Biopsies collected at day 14 revealed that APP-treated abutments exhibited significantly reduced inflammatory infiltrate, higher collagen density, and elevated expression of E-cadherin, a key epithelial adhesion molecule. Scanning electron microscopy further indicated dense fibroblast attachment and well-organized collagen networks in the APP group, whereas untreated surfaces lacked fibrous integration [77].

The potential for clinical translation of various such technologies has been increasingly explored in human studies, including small-scale clinical trials and biopsy analyses, as illustrated in Table 2. While early findings, particularly for laser-treated and plasma-treated surfaces, have shown improved soft tissue responses, further large-scale, long-term investigations are needed to establish definitive clinical efficacy.

#### 4.1.2. Nano-surface features

Nanoscale features, such as nanopores, nanotubes, and nanogrooves, regulate cellular behaviors including adhesion, proliferation, differentiation, and inflammatory responses. For example, mechanically created nanogrooves (0.1–0.2 μm) and keratin-based nanofibers fabricated via electrospinning have shown promise in improving the behavior of HGFs. These nano-architectures not only facilitate greater cellular adhesion and spreading but also contribute to anti-bacterial performance by reducing *S. aureus* colonization [85]. Such dual-functional responses are crucial for the long-term stability of the peri-implant mucosa.

Laser-engineered nanopores present another effective strategy for surface nano-modification. In an in vivo study by Ghinassi et al., gingival tissues surrounding laser-treated titanium abutments exhibited lower expression of pro-inflammatory cytokines and MMP9, alongside increased expression of desmosome proteins such as desmoglein-3. These molecular changes were associated with a more intact epithelial barrier and a reduced inflammatory profile compared to machined-surface abutments, indicating the enhanced epithelial sealing and immunomodulatory potential of nanoporous surfaces [74].

Building upon the anti-inflammatory potential of nanostructures, Julien et al. demonstrated that oxidation-induced microbead-like porous surfaces on titanium substrates could upregulate anti-inflammatory cytokines like IL-1RA and downregulate pro-fibrotic markers such as chemokine ligand 18. The treated surfaces also promoted the secretion of TGF-β, creating an environment conducive to tissue repair and integration. Over time, these pores were partially covered by host tissue, supporting their role in facilitating stable soft tissue attachment [86].

Emerging studies have also begun to explore the synergy between nano-topography and electrical stimulation therapy. One such approach [87] involves converting anodized $TiO_2$ nanopores into conductive titanium nanopores via magnesiothermic reduction. These conductive structures enabled the application of low-voltage electrical stimulation (1.5 V for 5 min daily), which significantly enhanced HGFs proliferation and collagen secretion while simultaneously reducing salivary biofilm formation. This "smart" implant concept integrates structural and functional cues to promote soft tissue healing while preventing bacterial colonization, paving the way for future implant designs with on-demand therapeutic capabilities.

The role of nanotopography in regulating cellular gene expression was emphasized by increased expression of the Mohawk gene in gingival fibroblasts cultured on $TiO_2$ nanopores. Since Mohawk gene plays a crucial role in ECM synthesis and tissue remodeling, its upregulation supports the mechanotransductive influence of nanoscale surfaces in driving soft tissue regeneration [87].

Titania nanotubes (TNTs) fabricated through electrochemical anodization demonstrated size-dependent effects on both soft tissue cell

**Table 2**
Summary of clinical studies evaluating surface treatments and coatings for peri-implant STI.

| Surface Treatment/Coating | Study Design | Sample Size | Key Outcomes | References |
|---|---|---|---|---|
| Titanium oxide-coated abutments | Randomized controlled trial (RCT) | 20 patients | Enhanced soft tissue healing and reduced inflammation compared to machined abutments | [78] |
| HA nano-coated SLA implants | RCT | 30 patients | Improved soft tissue attachment and reduced inflammatory markers at 4 months post-implantation | [79] |
| Anodized titanium abutments with anatase phase | RCT | 30 patients | Reduced bacterial adherence and promoted keratinized tissue formation | [80] |
| Plasma-treated titanium abutments | RCT | 25 patients | Reduced plaque accumulation and improved mucosal health | [77] |
| Argon plasma-treated titanium abutments | RCT | 30 patients | Reduced peri-implant bone loss in patients with thin gingival biotype and history of periodontal disease | [81] |
| Argon plasma-treated healing abutments | RCT with histological assessment | 30 patients | Enhanced soft tissue healing, reduced inflammation, and improved collagen integration at 2 months post-abutment placement | [82] |
| Plasma of argon cleaning procedure | Randomized Controlled Histologic Study | 30 patients | Improved cell adhesion, reduced bacterial contamination, and better collagen fiber orientation in plasma-treated abutments | [83] |
| Laser-microstructured titanium abutments | RCT | 20 patients | Enhanced soft tissue sealing and collagen fiber orientation with laser-microstructured abutments | [84] |

behavior and bacterial adhesion. TNTs with a diameter of ~100 nm significantly promoted HGFs adhesion, proliferation, and ECM-related gene expression while simultaneously suppressing the adhesion of *Porphyromonas gingivalis*. [70,88]. This finding highlights the importance of precise nanotube dimensioning in achieving a balance between cellular compatibility and antibacterial function, both critical for long-term peri-implant tissue health.

Furthermore, anodization treatments that create nanotubular and nanoporous architectures also alter the surface chemistry of titanium. Compared to conventionally turned surfaces, anodized surfaces exhibit increased Ti(IV) content and improved hydrophilicity, which further enhances protein adsorption and subsequent cellular responses [89]. The combination of altered chemical composition and nanoscale topography provides a more favorable interface for soft tissue attachment and may help mitigate the risk of peri-implant infections.

### 4.2. Surface coatings

Surface coatings differ from physical modification methods in that they involve applying a distinct bioactive layer onto the implant surface rather than altering its topography. While surface topography modification primarily changes micro- and nanoscale textures to influence cell attachment, coatings provide biochemical signals that can actively promote tissue integration and modulate the biological environment. These coatings are generally categorized as organic, such as peptides and ECM components that enhance cell adhesion and reduce inflammation, and inorganic, including materials like HA and titanium dioxide, which improve surface wettability and offer antimicrobial benefits. By integrating biochemical cues with physical surface features, coatings provide a complementary approach to optimize soft tissue healing around implants.

#### 4.2.1. Organic coating

Organic coatings on implant surfaces have emerged as a promising strategy to enhance STI by promoting epithelial and fibroblast adhesion, modulating inflammation, and improving cellular responses at the implant-soft tissue interface. One effective approach involves biofunctionalization with ECM proteins or peptides, such as laminin-332 and cell-adhesion motifs, which facilitate keratinocyte and fibroblast attachment via hemidesmosome formation (Table 3).

For example, laminin-332-coated titanium surfaces show nanoscale surface modifications that improve keratinocyte adhesion and spreading [90]. These surfaces also stimulate the secretion of key cytokines (e.g., IL-1α, IL-8) and growth factors (e.g., EGF, VEGF), essential for epithelial repair and tissue regeneration [90]. This biofunctionalization strategy enhances cell attachment and supports the biological signaling necessary to establish a stable soft tissue seal.

Polydopamine (PDA) coatings have garnered substantial interest owing to their strong substrate adhesion, intrinsic biocompatibility, and exceptional versatility as a platform for biofunctionalization. For instance, a recent study demonstrated that functionalizing zirconia implants with RGD (cell-adhesion) peptides via PDA coatings significantly enhanced HGFs adhesion and mitigated bacterial colonization, critical for dental implant success [99]. As depicted in Fig. 4A, PDA films, formed by dip-coating zirconia in dopamine solution at pH 8.5, provided a stronger platform for immobilizing linear or cyclic RGD peptides. Confocal microscopy (Fig. 4B) revealed more pronounced actin organization and larger cell spreading areas on RGD-modified surfaces. Among the two peptide formats, cyclic RGD ($ZrO_2$–P/C) showed marginally superior performance, attributed to its conformational rigidity and stronger binding affinity to integrin receptors such as αvβ3 and αvβ5. Additionally, the study assessed bacterial adhesion using *Streptococcus mutans* and *Porphyromonas gingivalis*, finding that both PDA and RGD-functionalized surfaces reduced bacterial colonization relative to unmodified zirconia. Importantly, the enhancement of fibroblast activity did not compromise the antibacterial potential of the surface, highlighting the dual biofunctional benefits of the approach.

**Table 3**
Peptides implicated in promoting peri-implant STI.

| Peptide Name | Sequence | Function/Role | Reference |
|---|---|---|---|
| Metal Binding Peptide 1 (MBP-1) | SVSVGMKPSPRP | Bioengineered peptide enhancing epithelial adhesion to titanium-based implants | [91] |
| Metal Binding Peptide 2 (MBP-2) | WDPPTLKRPVSP | Similar function as MBP-1; improves epithelial interaction with metal surfaces | [91] |
| Synthetic Peptide A10 | CGPPPGNPKIKWPPGGPC | Promotes epithelial cell adhesion and migration with reduced inflammatory response | [92] |
| Histatin | HEKRHHGYRRKFHEKH | Enhances attachment and spreading of oral epithelial cells and fibroblasts on titanium surfaces | [93] |
| RGD Peptides | Linear: KGGRGDSP<br>Cyclic: RGDfK | Mediate adhesion of (HGFs); commonly used in coatings to promote soft tissue cell attachment | [94,95] |
| Laminin-derived Peptide (Lam) | PPFLMLLKGSTRFC | Derived from laminin-332; enhances keratinocyte attachment via integrin α3β1 binding | [90] |
| Laminin-5 α3 Chain Peptide | PPFLMLLKGSTR | Facilitates epithelial tissue attachment to titanium; supports peri-implant epithelial sealing | [96] |
| D-amino acid K122-4 Peptide | ACTSNADNKYLPKTCQT | Enhances proliferation and alignment of HGFs; contributes to reduced bacterial colonization | [97,98] |

PDA coatings have also been explored as a vehicle for immunomodulation. For instance, Liu et al., investigated an immunomodulation-based strategy to enhance soft tissue integration around metal implants. Interleukin-4 (IL-4) was immobilized on titanium surfaces using a PDA coating, which served as a bioadhesive interlayer. In a rat model, bilateral maxillary first molars were extracted, and after a 4-week healing period, micro-implants were placed. The surrounding soft tissue was sutured, and complete mucosal healing was observed within 2 weeks post-implantation (Fig. 5A and B). Histological analysis revealed organized epithelial layers aligned parallel to the implant surface in all groups, with IL-4/PDA-coated implants showing enhanced tissue responses. Immunohistochemical staining demonstrated increased expression of CD206, a marker of M2 (pro-healing) macrophages, and laminin-5α3, a hemidesmosome-associated protein critical for epithelial adhesion (Fig. 5C and D&E). These findings indicated that IL-4-functionalized surfaces promoted favorable immune polarization and epithelial attachment, leading to improved soft tissue integration. Mechanistically, the IL-4/PDA coating activated the FAK–AKT–mTOR signaling pathway, as demonstrated by increased phosphorylation of pathway proteins. This activation, coupled with enhanced IGF-1 secretion, synergistically promoted epithelial cell proliferation, extracellular matrix deposition, and hemidesmosome assembly, contributing to improved soft tissue integration around the metal implants [100]. This study thus provides a strong evidence for the use of cytokine-functionalized coatings to modulate local immune responses and enhance the long-term stability of transmucosal metal implants.

Similarly dual-functional PDA coatings to both reduce inflammation and enhance tissue integration around implants have been engineered. By combining anti-inflammatory agents like conjugated linoleic acid

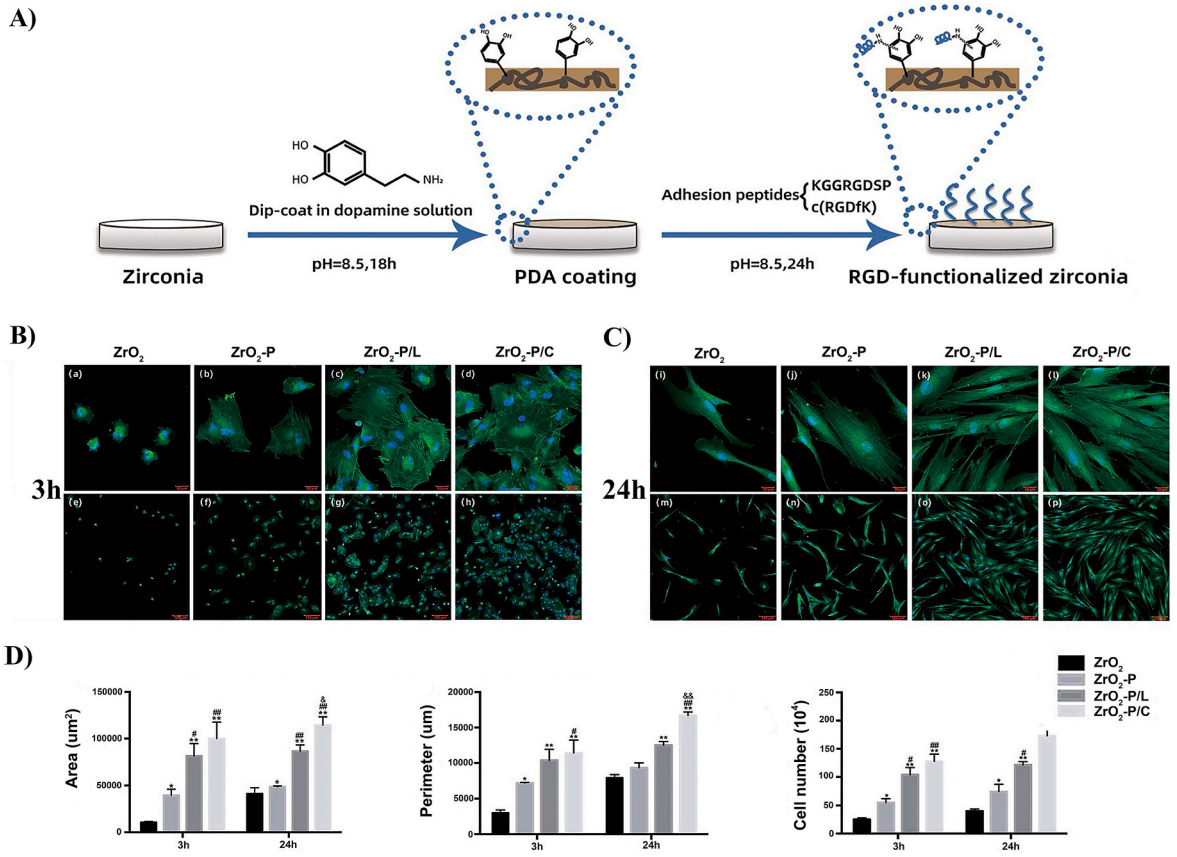


**Fig. 4.** Enhanced adhesion of HGFs and reduced bacterial colonization on RGD-modified zirconia surfaces. (A) Schematic illustration of the immobilization of RGD peptides on zirconia surfaces via PDA coating. (B, C) Confocal laser scanning microscopy images of HGFs cultured on various zirconia substrates for 3 h (B) and 24 h (C), including pristine zirconia ($ZrO_2$), PDA-modified zirconia ($ZrO_2$–P), linear RGD peptide-functionalized zirconia ($ZrO_2$–P/L), and cyclic RGD peptide-functionalized zirconia ($ZrO_2$–P/C). High-magnification insets (a–d, i–l) highlight cytoskeletal actin filaments (green) and cell nuclei (blue). (D) Quantitative analysis of HGF spreading area, cell perimeter, and cell count after 3 h and 24 h of culture on the different surfaces. Reproduced with permission from Ref. [99]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

with keratinocyte-adhesive peptides, these coatings downregulate pro-inflammatory macrophage markers while promoting hemidesmosome protein expression in oral keratinocytes, strengthening epithelial attachment [101]. Additionally, PDA's photothermal properties enable mild hyperthermia under near-infrared light, which boosts gingival fibroblast proliferation and collagen production. This photothermal effect also increases surface roughness and hydrophilicity, improving cell–material interactions and providing targeted antibacterial activity, making PDA coatings promising multifunctional candidates for peri-implant therapy [102].

Other organic strategies focus on harnessing platelet activation mechanisms to stimulate soft tissue healing. For instance, zirconia surfaces functionalized with platelet-activating peptides (e.g., PAR4) promote platelet aggregation and growth factor release (e.g., PDGF-AB), which enhances epithelial cell attachment and basal lamina formation. This biomimetic approach mimics natural wound healing processes, strengthening the biological seal at the implant–tissue interface [103].

Furthermore, multifunctional coatings incorporating peptides—beyond individual biomolecule immobilization—are gaining attraction for their ability to simultaneously promote epithelial attachment, modulate immune responses, and prevent bacterial colonization. For example, a recent study employed the co-immobilization of a designer antimicrobial peptide (AMP), GL13K, with a hemidesmosome-inducing laminin-derived peptide, LamLG3, on implant surfaces [104]. The surface fractional area of each peptide was modulated to achieve synergistic functionality. These peptide-functionalized surfaces exhibited potent antibiofilm activity against *Streptococcus gordonii* while enhancing proliferation, hemidesmosome formation, and mechanical attachment of oral keratinocytes. Interestingly, these multifunctional coatings selectively activated keratinocytes without affecting gingival fibroblasts—cells known to impede soft tissue seal formation. The coatings demonstrated high durability against thermochemical and mechanical challenges, indicating their potential intraoral longevity. This example highlights how AMPs such as GL13K can serve as dual-functional agents, contributing not only to antimicrobial defense but also to epithelial integration when used in co-functionalized designs [34,104].

AMP can also be engineered into self-assembled nanostructures for enhanced functionality. In one approach, GL13K amphiphilic nanostructures were synthesized and decorated with silver nanoparticles (AgNPs) to create enhanced antimicrobial nanocoatings on etched titanium (eTi) surfaces [105]. The strong hydrogen bonding between the polar eTi surface and the AMP amphiphiles yielded durable and adherent coatings. Compared to mono-component coatings with either AMP or AgNPs alone, these AgNP/AMP hybrid nano-coatings exhibited significantly higher antimicrobial efficacy in vitro against several bacterial strains relevant to implant-associated infections. Importantly, in vivo validation using a subcutaneous rat infection model confirmed their antibacterial performance, underscoring the translational relevance of such hybrid strategies in preventing peri-implant infections [105].

Moreover, graphene oxide (GO) has emerged as a promising platform for hybrid AMP-based coatings. In one study, the AMP Nal-P-113 was loaded onto GO-coated titanium surfaces to create a slow-release,

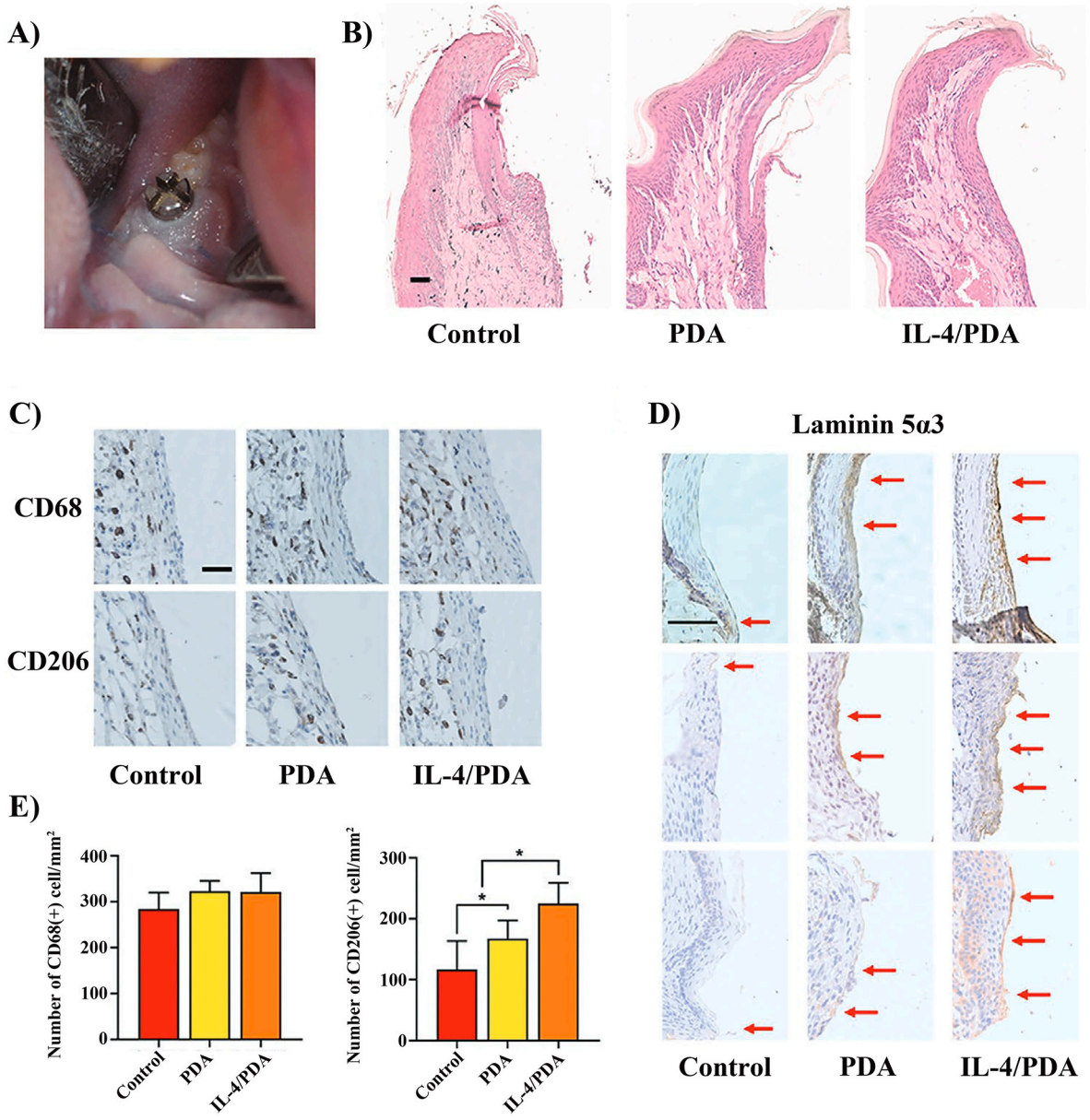


**Fig. 5.** Immunomodulatory effects of IL-4/PDA-coated Ti-alloys on macrophage polarization and peri-implant tissue integration. (**A**) Micro-implants were placed in rats, and the surrounding soft tissues were sutured. Complete mucosal healing was observed 2 weeks after implantation. (**B**) H&E staining revealed re-epithelialization around the implants in all groups, with epithelial layers aligned parallel to the implant surface and lacking rete pegs—suggesting orderly and stable epithelial attachment. (**C, D, and E**) Immunohistochemical staining and semi-quantitative analysis showed expression of CD68 (pan-macrophage marker), CD206 (M2 macrophage marker), and laminin-5α3 (a hemidesmosome-associated protein), indicating favorable M2 macrophage polarization and enhanced epithelial anchorage. Adapted from Ref. [100].

antibacterial system effective against both *Streptococcus mutans* and *Porphyromonas gingivalis* [106]. These coatings also maintained cytocompatibility with gingival fibroblasts. In another example, reduced GO–silver nanocomposites were functionalized with poly-L-lysine (PLL), a cationic AMP, producing hybrid materials that inhibited *Staphylococcus aureus* biofilm formation [107]. These GO–peptide systems offer a unique combination of mechanical reinforcement, high surface area for drug loading, and controlled release profiles, making them promising candidates for multifunctional coatings that couple antimicrobial, bioactive, and mechanical functions in a single platform.

#### 4.2.2. Inorganic coating

Achieving a reliable soft tissue seal around dental implants requires more than surface biocompatibility—it necessitates the active modulation of epithelial and connective tissue behavior. Strategies like atomic layer deposition (ALD) of HA offer not only compositional mimicry of native bone and tooth structures but also the precision to coat complex geometries without altering the underlying microtopography. ALD-HA coatings have demonstrated enhanced expression of key adhesion molecules such as laminin γ2 and increased peripheral hemidesmosome formation, both of which are crucial for stable epithelial attachment. These effects were observed in 2D in vitro cultures of human gingival keratinocytes, where ALD-HA surfaces significantly promoted cell adhesion, spreading, and proliferation compared to uncoated titanium. The findings underscore the potential of ALD-HA coatings to improve soft tissue integration around dental implants [108].

While ALD represents a bioinspired approach, other strategies are designed to provide multifunctionality to support tissue integration and prevent bacterial colonization. A striking example is the co-treatment of implant surfaces with strontium acetate and silver nitrate [109]. This

combination leverages strontium's capacity to enhance fibroblast migration and silver's broad-spectrum antimicrobial activity. The study evaluating this dual-modified surface went beyond standard in vitro assays, employing a 3D tissue-engineered oral mucosa model, which allowed for a more physiologically relevant assessment of epithelial integrity and connective tissue response. In this model, strontium acetate mitigated the cytotoxic effects of silver nitrate, preserving epithelial continuity while still conferring antibacterial properties.

Furthermore, graphene oxide (GO)-mineralized collagen constructs represent a new wave of biofunctional surfaces with responsive antimicrobial capabilities. These constructs utilize the photothermal properties of GO to disrupt biofilms upon near-infrared light activation, while the mineralized collagen component supports cell adhesion and ECM formation. This approach was shown to maintain epithelial viability and promote focal adhesion protein expression, even under photoactivation stress [110]. Though currently explored in vitro, these systems pave the way for the development of smart surfaces with switchable functionalities, responsive to dynamic oral environments.

Emerging inorganic nanomaterials, such as copper-doped mesoporous bioactive glass (Cu-MBG) and nanoceria ($CeO_2$), have introduced a new dimension of functionality to implant surface engineering, enabling ion-mediated bioactivity with extended regulatory effects on oxidative stress and inflammatory signaling [111].

Notably, nanoceria's intrinsic reactive oxygen species (ROS) scavenging ability has been associated with enhanced fibroblast adhesion and upregulation of ECM gene expression in vitro. [113]. Building on these functional capabilities, recent studies demonstrated the synergistic efficacy of multi-component nano-coatings that integrate Zn–Sr bioactive glass, ceria nanoparticles, and conventional bioglass. Fig. 6A shows, through transcriptomic analysis, that Zn-SrBG/ceria coatings significantly modulated gene expression patterns associated with regenerative pathways. Notably, there was marked upregulation of genes linked to hypoxia signaling, angiogenesis, endothelial cell migration, and extracellular matrix remodeling, indicating the coating's ability to create a pro-angiogenic and pro-healing microenvironment. These findings were consistent with enhanced endothelial tube formation and accelerated fibroblast migration observed in functional assays (Fig. 6B), underscoring the composite coating's therapeutic potential for promoting both vascularization and soft tissue repair [112].

Collectively, these studies exemplify a growing trend toward multimodal validation, where promising materials and surface strategies are evaluated not only in simple in-vitro systems but also in 3D models, animal studies, and human clinical settings. This layered approach strengthen confidence in the clinical relevance of findings, reflecting a maturing field increasingly focused on translational outcomes. As surface modification technologies advance, the integration of mechanistic insights from molecular biology with multi-tiered biological models will be crucial in developing implant surfaces that actively support long-term soft tissue health and stability.

### 4.3. *Soft tissue integration in medically compromised conditions*

Beyond surface-modification techniques for enhancing STI, it is crucial to examine their performance under medically compromised conditions, such as diabetes and osteoporosis, where altered biological environments can influence implant success. Post-implant soft tissue

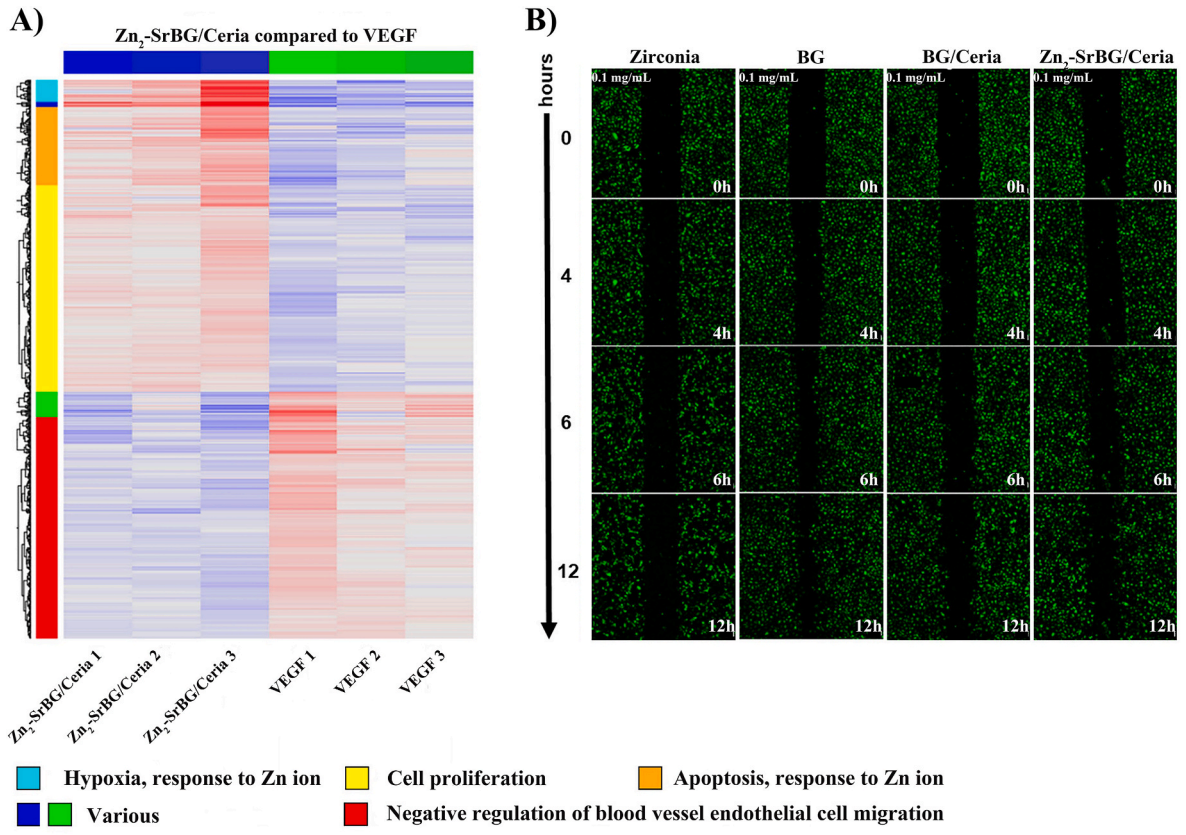


**Fig. 6.** Porous bioactive coatings incorporating Zn-SrBG/ceria nanoparticles for enhanced soft tissue regeneration and antimicrobial efficacy. **(A)** Endothelial cells from the VEGF and Zn-SrBG/ceria nanoparticle treatment groups were pooled and analyzed by comparative transcriptomic clustering. Compared to VEGF treatment, Zn-SrBG/ceria nanoparticles notably induced a hypoxia response, which is known to promote angiogenesis and also upregulated genes related to blood vessel cell migration, increased cell differentiation, and apoptosis, suggesting cellular reorganization and a specific response to zinc ions. **(B)** The effects of different nanoparticles on normal human dermal fibroblast migration and proliferation were assessed using a 12-h scratch assay. Bioglass (BG) nanoparticles promoted faster wound closure and also enhanced the effects of the composite nanoparticles. Adapted from Ref. [112].

healing is often significantly impaired in patients with chronic systemic diseases like diabetes mellitus and osteoporosis, primarily due to disruptions in the peri-implant microenvironment. In diabetes, chronic hyperglycemia compromises fibroblast function, collagen synthesis, and angiogenesis, leading to delayed wound healing and increased susceptibility to inflammation and infection [114]. Additionally, advanced glycation end-products further disrupt cell–matrix interactions and perpetuate a pro-inflammatory milieu. While osteoporosis primarily affects bone turnover, it also negatively impacts soft tissue healing by reducing vascularization and dysregulating immune responses [115,116]. Both conditions are marked by impaired angiogenesis and a pathological shift in macrophage polarization toward the pro-inflammatory M1 phenotype, which delays wound resolution [116,117]. As stable mucosal seal around implants is essential to prevent microbial invasion and peri-implantitis, improving soft tissue integration in these high-risk populations is a critical unmet need.

While most current research targets osseointegration, a few promising surface coatings have emerged with relevance to STI, particularly through promoting angiogenesis, supporting epithelial attachment, and modulating immune responses. For instance, magnesium-incorporated coatings have shown potential to enhance angiogenesis and M2 macrophage polarization in hyperglycemic environments, thereby supporting mucosal healing [118]. Similarly, smart titanium coatings for localized carbon monoxide delivery promote vascularization and soft tissue integration, while also offering switchable antibacterial and immunomodulatory effects [119].

Another example is the zinc-containing chitosan/gelatin coating, which enhances fibroblast proliferation and promotes an M2 immune response, aiding in STI [120]. Additionally, dual-function coatings that simultaneously promote keratinocyte attachment and suppress inflammation offer a balanced strategy to reinforce epithelial sealing while managing the immune response at the transmucosal interface [101].

Although these coatings were not specifically evaluated under diabetic or osteoporotic conditions, their mechanisms of action directly address pathophysiological features common to both: impaired angiogenesis, chronic inflammation, and compromised tissue remodeling. As such, these strategies represent promising candidates for future adaptation and evaluation in medically compromised models. Ultimately, bridging this research gap by tailoring coatings to the specific challenges of systemic diseases could significantly improve soft tissue outcomes and long-term implant success in medically compromised populations.

## 5. Conclusions and future perspectives

STI remains a linchpin in the long-term success of dental implants, acting as both a mechanical barrier and a biological interface that shields the peri-implant environment from bacterial invasion and inflammatory insult. To date, no dental implants have been marketed exclusively for the purpose of promoting STI. Most commercially available implants are designed primarily to achieve osseointegration, with soft tissue responses addressed indirectly through abutment design or surface modifications at the transmucosal region. Systems such as Straumann® SLActive and Roxolid® implants improve hydrophilicity and biocompatibility to benefit both bone and soft tissue, while Zimmer Biomet's Laser-Lok® technology promotes collagen fiber attachment, more closely mimicking natural periodontal architecture [121,122]. Although these implants are not marketed solely for STI, they demonstrate some promising clinical outcomes by enhancing epithelial and connective tissue attachment, reducing marginal bone loss, and lowering inflammatory responses around the implant neck. This reflects an important shift in implant design philosophy — from focusing exclusively on osseointegration to embracing multifactorial biological integration where soft tissue behavior is actively considered.

The absence of implants designed exclusively for STI can be attributed to the complex biology of soft tissues, the lack of standardized, predictive evaluation models, and regulatory challenges in validating long-term soft tissue outcomes. To propel the commercial development of STI-specific implants, several strategies should be prioritized: biomimetic surface engineering of the transmucosal zone to promote fibroblast alignment and collagen deposition; incorporation of bioactive coatings such as laminin-derived peptides and anti-inflammatory cytokines; immunomodulatory surface tuning to encourage pro-regenerative macrophage polarization; and multiphase implant designs with region-specific surface properties tailored to bone and soft tissue compartments.

Moving forward, the field must embrace a paradigm shift from passive compatibility toward active, multifunctional interfaces that coordinate host tissue integration with on-demand antimicrobial defense. Key research trajectories include.

1. Engineered, triggered antimicrobial release: Engineered triggered antimicrobial drug release is a promising approach for enhancing STI. By enabling controlled and responsive drug delivery, this strategy ensures that antimicrobial agents are released precisely when needed (e.g. during bacterial colonization or inflammation) without continuous exposure that might lead to resistance or tissue toxicity. This dynamic system not only improves infection prevention but also promotes STI, reducing the risk of peri-implantitis and ensuring the long-term success of the implant.
2. Perpendicular collagen fiber deposition: Current techniques primarily result in collagen fibers being deposited parallel to the surfaces of implants and abutments, leading to weaker STI. In contrast, perpendicular collagen fiber alignment replicates the natural PDL structure found around teeth, establishing a strong and stable interface between the soft tissue and the implant surface. This enhanced fiber orientation prevents bacterial invasion to support the long-term health of peri-implant tissues. Therefore, future research should prioritize the development of innovative approaches that facilitate the formation and insertion of perpendicular collagen fibers into implant and abutment surfaces.
3. Holistic in vitro and in vivo models incorporating patient-specific factors:
   Traditional monocultures of gingival fibroblasts fall short in capturing the intricate cellular interactions among keratinocytes, endothelial cells, immune effectors, and oral microbiota. To better mimicking pathophysiological environment, future models need to integrate advanced 3D organotypic cultures and microfluidic "oral-on-a-chip" platforms that simulate saliva flow and include defined microbial communities. Importantly, these systems can offer the potential to incorporate patient-specific factors such as systemic conditions (e.g., diabetes, osteoporosis), which significantly impact STI but are often overlooked in current experimental designs.
4. Patient-specific, functionally graded implants: These implants can be fabricated using advanced additive manufacturing techniques, allowing for spatial variations in composition and microarchitecture—dense cores for load-bearing capacity, porous regions to facilitate bone ingrowth, and specialized soft tissue–engineered surfaces with antimicrobial functionality. Computational tools, informed by patient-specific anatomy and microbiome profiles, will enable tailored implant designs that optimize tissue integration. By customizing the implant structure to individual patient characteristics, functionally graded implants enhance biomechanical compatibility, promote stable soft tissue attachment, and minimize inflammatory responses.
5. Microbiome-informed therapeutics: Microbiome-informed therapies precisely modulate the peri-implant microbiome to help maintain a balanced microbial environment that supports tissue health and integration. By leveraging insights into the oral microbiome, these therapies can selectively promote beneficial bacterial populations while inhibiting pathogenic microbes that contribute to inflammation and peri-implant diseases. This targeted approach not only

strengthens STI but also minimizes complications associated with bacterial imbalance.

6. Long-term clinical surveillance and standardization: The field faces a lack of standardized protocols with studies employing widely varying methodologies, including histological analyses and cell-based assays, while often using different outcome metrics. This heterogeneity impedes direct comparison and meta-analysis across studies, limiting the ability to draw consistent conclusions. To overcome these challenges, future research should integrate advanced, physiologically relevant models with standardized evaluation frameworks and personalized variables. Additionally, long-term clinical surveillance through extended in vivo studies beyond 12 months, complemented by standardized implant registries tracking soft tissue parameters, microbial colonization, and implant integrity, is essential. These comprehensive and uniform approaches will deepen our understanding of failure modes and drive the development of improved implant designs that achieve better STI.
7. Regulatory and manufacturing pathways: Collaborative efforts with regulatory bodies are essential to establish rigorous criteria for antimicrobial efficacy, biocompatibility, and mechanical stability in dental implants. Clear guidelines ensure that implants meet safety standards to effectively promote STI and reduce infection risks. Additionally, the development of scalable manufacturing methods is crucial for ensuring consistency, reproducibility, and cost-effectiveness. Advanced fabrication techniques, such as additive manufacturing and surface bioengineering, enable precise control over implant properties to enhance tissue integration. By streamlining regulatory approval processes and optimizing production, these efforts will accelerate clinical adoption and improve long-term outcomes.

In summary, the next generation of dental implants will go beyond the concept of inert fixtures, evolving into active, intelligent platforms that facilitate tissue healing, pathogen defense, and adaptation to individual biological profiles. By integrating advancements in materials science, immunology, microbiology, and digital design, these implants will offer superior STI, significantly lower peri-implantitis rates, and usher in a new era of personalized oral rehabilitation.

## CRediT authorship contribution statement

**Revathi Alexander:** Writing – original draft, Investigation. **Xiaohua Liu:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

This work was partially supported by R01DE029808, R01DE032540, and R01DE034978 (X.L).

## Data availability

No data was used for the research described in the article.

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