International Journal of Nanomedicine

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REVIEW

Surface Topography Steer Soft Tissue Response and Antibacterial Function at the Transmucosal Region of Titanium Implant

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Abstract: Metallic dental implants have been extensively used in clinical practice due to their superior mechanical properties, biocompatibility, and aesthetic outcomes. However, their integration with the surrounding soft tissue at the mucosal region remains challenging and can cause implant failure due to the peri-implant immune microenvironment. The soft tissue integration of dental implants can be ameliorated through different surface modifications. This review discussed and summarized the current knowledge of topography-mediated immune response and topography-mediated antibacterial activity in Ti dental implants which enhance soft tissue integration and their clinical performance. For example, nanopillar-like topographies such as spinules, and spikes showed effective antibacterial activity in human salivary biofilm which was due to the lethal stretching of bacterial membrane between the nanopillars. The key findings of this review were (I) cross-talk between surface nanotopography and soft tissue integration in which the surface nanotopography can guide the perpendicular orientation of collagen fibers into connective tissue which leads to the stability of soft tissue, (II) nanotubular array could shift the macrophage phenotype from pro-inflammatory (M1) to anti-inflammatory (M2) and manipulate the balance of osteogenesis/osteoclasia, and (III) surface nanotopography can provide specific sites for the loading of antibacterial agents and metallic nanoparticles of clinical interest functionalizing the implant surface. Silver-containing nanotubular topography significantly decreased the formation of fibrous encapsulation in per-implant soft tissue and showed synergistic antifungal and antibacterial properties. Although the Ti implants with surface nanotopography have shown promising in targeting soft tissue healing in vitro and in vivo through their immunomodulatory and antibacterial properties, however, long-term in vivo studies need to be conducted particularly in osteoporotic, and diabetic patients to ensure their desired performance with immunomodulatory and antibacterial properties. The optimization of product development is another challenging issue for its clinical translation, as the dental implant with surface nanotopography must endure implantation and operation inside the dental microenvironment. Finally, the sustainable release of metallic nanoparticles could be challenging to reduce cytotoxicity while augmenting the therapeutic effects.

Keywords: dental implant, nanotopography, roughness, macrophage, immunomodulation, biofilm formation

Introduction

Dental implants are known as the most advanced solution to repair teeth loss. Although dental implants can improve people's quality of life, infection and separation of the implants are the main critical issues that must be carefully

Received: 9 February 2024
Accepted: 10 April 2024
Published: 27 May 2024

considered. The permanent teeth of adults will be lost as adults by increasing their age due to different reasons such as periodontal and gum diseases, failed root canals, and accidents. Thus, several dental implants are annually used to replace missing teeth.[1] The demand for specific treatment when the patient is seeking dental treatment has promoted investigations on biomaterials in the dental market.[2,3] The global dental implant market will reach 13.01 billion by 2023, from 9.5 $ billion in 2018.[4] Besides, the global market for dental prostheses is expected to reach over 5.7 billion USD by 2027.[5]

A dental implant is an artificial root placed into the jaw to hold the crown or support the prosthesis. Dental implants can be categorized into three main groups depending on their properties: (1) physicochemical properties, (2) topographic, and (3) mechanical.[6] The oral cavity is a complex biochemical and electrochemical environment comprised of inorganic ions such as chloride and hydrogen, bacteria, and organic constituents affecting the performance of the dental implant. Peri-implantitis and lack of proper osseointegration are among the main reasons for the failure of the dental implant. The integration between the implant and both hard and soft tissues determines the longevity of the dental implant.[7,8] The osseointegration between bone and the implant is the critical factor in the survival rate of the implant over some time. It indicates that rigid fixation is achieved and retained in the alveolar bone during loading.[9] The low osseointegration can cause micro-mobility of the implant which consequently leads to its failure. It was found that the peri-implant bone loss of 1 mm in the first year post-implantation and greater than 0.2 mm in the following year results in the failure of the dental implant.[10,11]

Titanium (Ti) has been widely used as a dental implant due to its superior biocompatibility.[12,13] Nonetheless, the integration of metallic implants with surrounding soft tissue is challenging.[14] This lack of proper soft tissue integration leads to metal implant failure due to peri-implant mucositis and peri-implantitis caused by tenacious immune response.[15,16] Alternatively, zirconia has been used as a dental implant because of its aesthetic features compared to Ti. Nevertheless, the surface inertness of zirconia affects its biological activity and subsequently its long-term stability as a dental implant.[17,18] Currently, a new paradigm implies that the osseointegration of dental implants is an immune-driven process leading to the formation of new bone formation surrounding the dental implant surface.[19] With this new concept, a tolerogenic balance could be established between the surface of the dental implant and the peri-implant tissue.[20,21] This indicates that the immune response can regulate tissue healing and play a vital role in the establishment of soft tissue integration around teeth.[22] Thus, a better understanding of osteoimmunology in the peri-implant environment is needed.

During the initial stage of dental implant development, the focus was mainly on the effect of surface modification at the microscale. However, it was recently shifted to the nano level.[23–26] Recently, biomaterials with nanoengineered structures have revealed promising results in oral rehabilitation using dental implants and endodontics to control intracanal contamination.[27–29] For this purpose, various methods can be used for surface modification of dental implants, including mechanical (blasting, grinding), chemical (acid-etching, anodization), and physical (plasma spraying). The readers are referred to references published elsewhere.[30–32] This review aims to focus on the role of surface engineering of dental implant surface on the modulation of the immune response, which leads to better performance of dental implants in clinical applications. It is hoped that this review provides a glimpse of current progress made in topography-modulated immunomodulation of dental implants to address the challenges in enhancing soft tissue integration and in turn clinical outcomes in patients receiving dental treatment. Fostering collaborations between material scientists, immunologists, and dental manufacturers can potentiate further discoveries in the coming days.

Clinical Challenge of Ti-based Implant

The clinical application dates back to the 1950s to the 1980s when Ti and its alloy were utilized as surgical implant material.[33] Ti has been known as a desirable material for dental implants.[34] Currently, commercially pure titanium (cpTi) and Ti-6Al-4V have found applications in dentistry as well.[35] Although a stable and dense oxide layer can be formed on the surface of Ti alloys rendering them good biocompatibility and corrosion resistance,[36] however, the biocorrosion or wear can damage this oxide layer which causes the release of metal ions.[37] As a consequence, the immune responses are triggered and implant failure occurs.[38] In dental applications, the chemical corrosion of Ti alloy due to environmental factors such as pH or bacteria can induce inflammatory responses. The bacterial adherence to the implant forms a periprosthetic biofilm layer which leads to local infection.[39] Furthermore, the implant wear debris can cause chronic

aseptic inflammation which in turn, leads to implant loss through peri-implant osteolysis.[40,41] The underlying mechanism for Ti alloys was suggested to be via RANK/RANKL.[42,43]

The macrophage polarization palsy has an important role in the inflammatory response of Ti implant after implantation. The surface characteristics of Ti implant such as roughness can influence the activation and polarization of macrophage. The particles of Ti alloy were found to cause granulomas as peri-implant lesions due to the secretion of TNF-α and IL-6 pro-inflammatory macrophage.[43,44] In addition, the release of IL-1 and TNF-α from macrophages can activate the osteolytic process of peri-implantitis.[45] Figure 1 depicts the Ti implant and the activated macrophages which cause inflammatory reactions. Thus, the surface modification of Ti alloys can shift the macrophage polarization from pro-inflammatory to anti-inflammatory mode and in turn, reduce inflammatory responses.[46]

Overview of Soft Tissue Integration

The soft tissue surrounding the osseointegrated implant is comprised of epithelium and other connective tissues both contribute to establishing soft tissue around the implants. The attachment of peri-implant soft tissue leads to wound healing.[47] For transmucosal constituents, the soft tissue structures, blood cells, and proteins dominate the interactions between cells and tissue with the substrate.[48] This indicates the complexity of interactions between the soft tissue cells and the substrate. The hemidesmosome structure mediates the adhesion of peri-implant epithelium (PIE) to the implant and inadequate hemidesmosome can weaken the attachment of PIE.[49,50] The subepithelial connective tissue contains a high content of collagen fibers.[51] The collagen fibers at one end are embedded in the natural cementum, and the other end is in the gingiva by which the tooth is connected with the connective tissue. The supraperiosteal artery and periodontal vessels supply the gingival connective tissue, whereas the branches of the superior periosteal artery supply the implant.[52] The peri-implant soft tissue has a similar structure to that of a natural periodontal tooth.[53] However, in terms of composition, orientation of collagen fibers, and the distribution of the vascular system, it is much more comparable to scar tissue.[54,55] The firm dental connective tissue integration is established by the projection of connective tissue fibers from the root cementum into the hard tissue. The collagen fibers in the periodontium are directly attached to the surface of the tooth and intertwined in several groups inside the connective tissue by which a more cohesive soft tissue attachment is formed.[56] This arrangement of collagen fibers is largely secreted and remodeled by gingival fibroblasts.[57] It should be noted that a small fraction of gingival fibroblasts contributes to

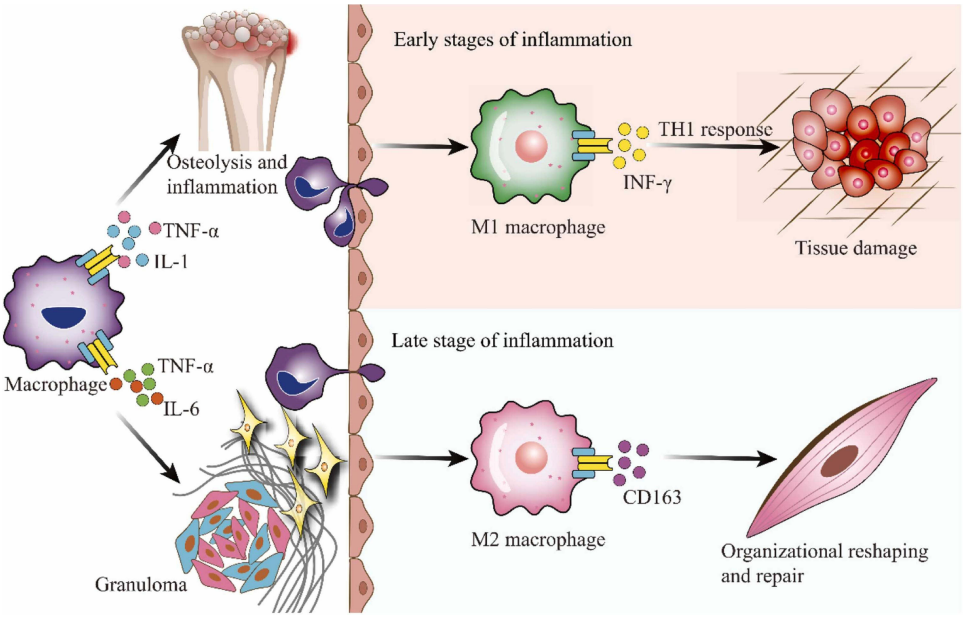

Figure 1 A schematic representation of Ti implants and activation of macrophages. The release of IL-1 and TNF-α activates osteolysis and peri-implantitis. M1 and M2 denote the pro-inflammatory and anti-inflammatory phenotype in the early and late stages of the inflammatory phase. Reprinted from *J Alloy Comp*, Volume: 977, Xu L, Wei C, Deng L, Wang P, Zhong W, Huang W. A review of non-biodegradable alloys implantation induced inflammatory and immune cell responses. 173086, Copyright 2024, with permission from Elsevier.[44]

attaining the transmucosal connective tissue integration with dental implants due to their remarkable lower numbers that can be found in periodontal connective tissue.[58] In addition, the lower amount of gingival fibroblasts as well as the lack of fiber connection to the surface of the implant causes a poor integrated transmucosal connective tissue.[59] The soft tissue integration around the dental implant was easily breached compared to that of natural teeth, which is mainly attributed to the lack of biological integration with the surface of the dental implant.[60,61] The insufficient soft tissue integration with the implant causes a persistent immunologic response by which chronic inflammation is created.[14] In addition, the lack of soft tissue integration may lead to implant failure due to peri-implantitis restricting the application of the implant.[15]

Previous studies documented the close connection between the immune microenvironment and soft tissue integration through regulating the adhesion of epithelial cells, synthesis of collagen, and the re-organization of connective tissues.[14,62,63] For instance, Chehroudi et al reported the presence of connective tissue ingrowth on the micromachined titanium screw, while they found a thick capsule and down growth of epithelial cells on the Ti smooth surface.[64] Therefore, the immune microenvironment can affect soft tissue integration and can be modulated by the surface properties of the implant.[65] The immune cells can promote the proliferation of fibroblasts as soft tissue cells through the secretion of specific factors. In addition, they remove debris from the wound site by phagocytosis and produce enzymes that help soft tissue reorganization (Figure 2a).[66] The first barrier against the invasion of bacterial pathogens is the strong soft tissue attachment. Nonetheless, the risk of bacterial adhesion is increased by a higher permeability of peri-implant soft tissue (Figure 2b and c).[55,67] This, in turn, exacerbates the inflammation associated with periodontitis. Moreover, the risk of peri-implantitis may also be increased in patients with periodontitis which is mediated by immune complexes in gingival tissue.[68] If the transmucosal barrier is breached, peri-implant mucosal inflammation and bone resorption occur, leading to implant failure. Thus, robust and stable soft tissue integration is required for the long-term functioning of the dental implant.

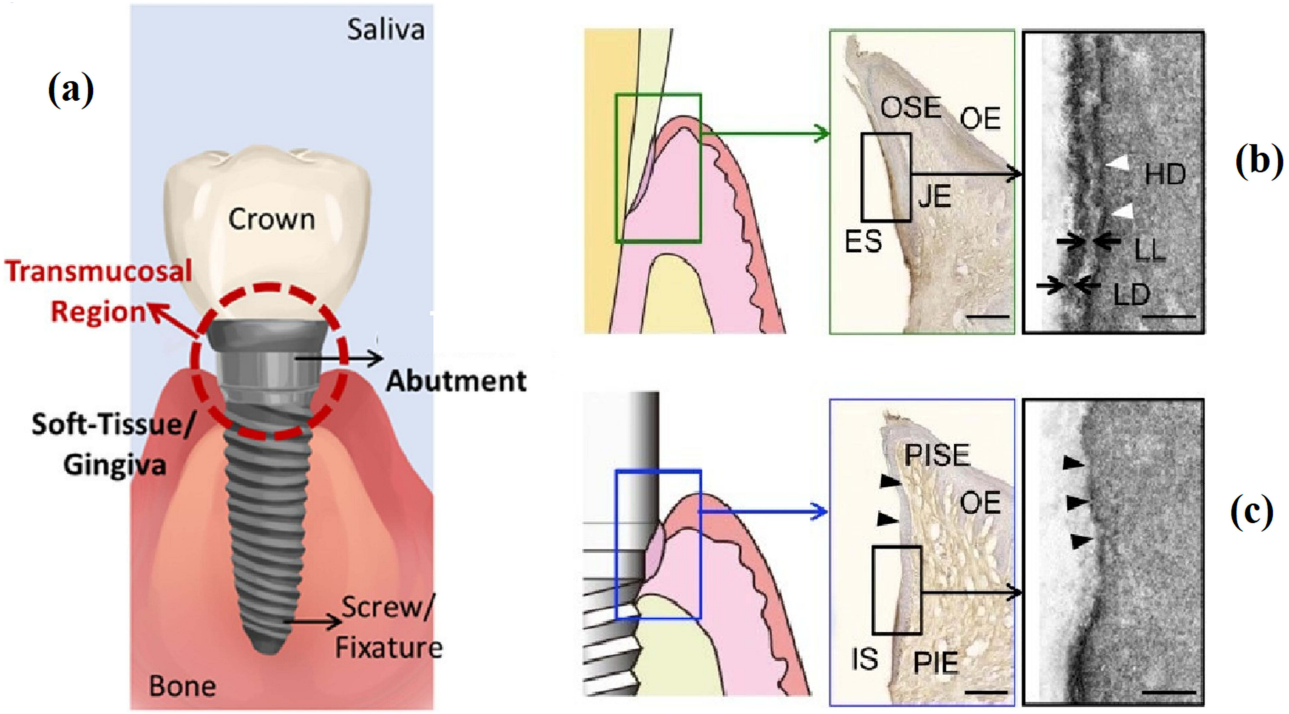

Figure 2 Schematic representation of (**a**) transmucosal region showing implant surface. Reprinted from *Acta Biomater*, Volume 124, Guo T, Gulati K, Arora H, Han P, Fournier B, Ivanovski S. Orchestrating soft tissue integration at the transmucosal region of titanium implants. 33–49, Copyright 2021, with permission from Elsevier.[58] (**b**) Histological staining of gingival, white arrowheads indicate hemidesmosome-like structure and black arrows indicate the normal appearance of periodontal tissue representing lamina densa and lamina lucida with a dual layer of anti-rat Laminin-322 (Ln) staining (**c**) Histological staining of peri-implant soft tissue. Black arrowheads represent the regions where the dual layer of Ln staining is not apparent. Reprinted from *J Prosthod Res*, Volume 60(1), Atsuta I, Ayukawa Y, Kondo R, et al. Soft tissue sealing around dental implants based on histological interpretation. 3–11, Copyright 2016, with permission from Elsevier.[67]
Abbreviations: OSE, Oral sulcular epithelium; PISE, peri-implant sulcular epithelium; PIE, peri-implant epithelium; OE, oral epithelium; JE, junctional epithelium respectively. RP, Reprinted with permission.

Engineering Topography of Ti Implant

The implant biomaterials are routinely placed to restore the function of damaged tissue. It is well recognized that the roughness in nanoscale or nanotopography on the implant surface plays an essential role in the regulation of cellular bioactivity. Additionally, the acceptance and long-term success of implants are influenced by two determining factors: integration and infection. Therefore, the focus of the literature research has been directed to ameliorating the implant-tissue integration and the ingress of bacteria into the implant site which leads to the minimization of infection.[69,70] The concept of nanotopography has emerged in biomaterial research referring to structural features which possess at least one dimension less than 100 nm in diameter.[71] During the initial stage of dental implant development, the focus was mainly on the effect of surface modification at the microscale. However, it was recently shifted to the nano level. Controlling the surface bulk properties and the interfacial reactions at the nanoscale plays an important role in developing dental implants, which lowers implant failure[11] and improves the integration with the surrounding tissue.[72] Various methods can be used for the nanostructured surface modification of dental implants, including photolithography,[73] electron beam lithography,[74] anodization,[75] phase separation,[76] and alkaline hydrothermal treatment.[77] A summary of these techniques is described in the following sections.

Photolithography

In photolithography, the source of radiation is ultraviolet (UV) light projecting the image of favored patterns on a photoresist surface. A mask comprising the pattern is coated with a material that is non-transparent to UV. The uncovered photosensitive becomes soluble and then is extracted by exposing it to a suitable solvent after irradiation. The structures with a dimension of 50 nm have been yielded by photolithography,[78] nonetheless, the diffraction limits make it difficult to fabricate nanostructures with a dimension smaller than 100 nm.[73] The nanogratings with a size of 600 nm have been yielded by this technique.[79]

Electron Beam Lithography

In electron beam lithography, the source of light is electrons which can overcome the constraints related to diffraction limits. The surface is first covered with an electron-sensitive material. The merit of this type of lithography is the high resolution. This technique could yield structures with a dimension in the range of below 100 nm.[74] The topographies comprising nanopits and nanodots with a size of 120 nm and 12 nm have been produced by this technique, respectively.[80,81] However, being costly, slow, and time-consuming are among the demerits of this technique.

Anodization

The addition of a natural oxide layer on the metallic surface or alloy through an electrochemical process is called anodization.[75] In this technique, the metal is connected to an anode followed by immersion in an electrolytic solution. In the next step, a current passes through the electrolytic solution which releases hydrogen and oxygen at the cathode and anode, respectively. This results in the generation of oxide nanocoating on the metal surface by random reactions at the surface of the metal. The topographies including nanopillars and nanotubes with a size of 15–100 nm have been fabricated by this technique.[82,83]

Phase Separation

The phenomenon of phase separation occurs when the maximum solubility of a compound (polymer blend) in a solvent is surpassed. The process phase separation is frequently controlled by the temperature of the solution. During phase separation, the mixture is separated into polymer-rich and polymer-thin ends. The polymer-rich end is then solidified by solvent removal.[84] Several topographical features such as nanodots (20 nm),[76] nanoislands (13 nm and 35 nm),[85] and dot- and worm-like nanopatterns (160 nm).[86] Nonetheless, the type of polymer, solution, concentration, as well as temperature can affect the resultant surface roughness.

Nanoimprinting

In the nanoimprinting technique, hot embossing of a nanostructure pattern is employed.[87] In this technique, a thin layer of thermoplastic polymer is coated on a substrate and then, pressed against the nanotopographically modified surface. The imprints of nanostructures are generated on the polymer by heating the polymer above its glass transition temperature. The topographies such as nanopits, nanogrooves, and nanograting have been yielded by this technique with a size of 50 nm, and 350, respectively.[88–90]

Role of Topography on Soft Tissue Integration

The manipulation of surface topography could lead to a promotion of cellular reactions for bone formation. The surface modification of Ti and Ti alloy substrates was found to improve their osteogenic properties.[91] The complexity of surface topography stimulates the osteogenic outcomes in which the variation in the responses was due to shape, chemistry, and nanotexture.[92,93] For example, Narimatsu et al have reported good epithelial attachment and good connective tissue bonding for smooth surfaces and rough surfaces in vivo, respectively.[94] Furthermore, a 10-year study that evaluated the performance of dental implants with roughness on a submicron scale revealed a survival rate of 98.9% and healthy soft tissue in patients suffering from per-implant inflammation.[95]

The biophysical cues possess an indispensable relationship with natural biosystems, and thus, they should be taken into account during the design of biomaterial designs for tissue integration.[96] One of the biophysical cues is surface topography which has been shown to affect the interaction between integrin and matrix (Figure 3).[61,97] The bone implant with topological modifications (surface roughness) has gained increasing attention as it is the main interface that influences the interactions between biomaterials and the host tissue. In general, the surface orientation and the surface roughness determine the surface topography.

The surface characteristic is known to affect cell proliferation, migration, and the orientation of collagen fibers. The initial cell and protein adhesion play a key role in achieving soft tissue integration. The enhancement in the protein adsorption could be obtained by timely transmucosal sealing. Furthermore, the stability of soft tissue can be guaranteed through the perpendicular orientation of collagen fiber in the connective tissue on the cementum. As a consequence, the underlying alveolar bone is protected against the stimulation from oral environment. Various strategies have attempted to improve the attachment of fibroblast cells, the adhesion of epithelial cells, and the promotion of connective tissue

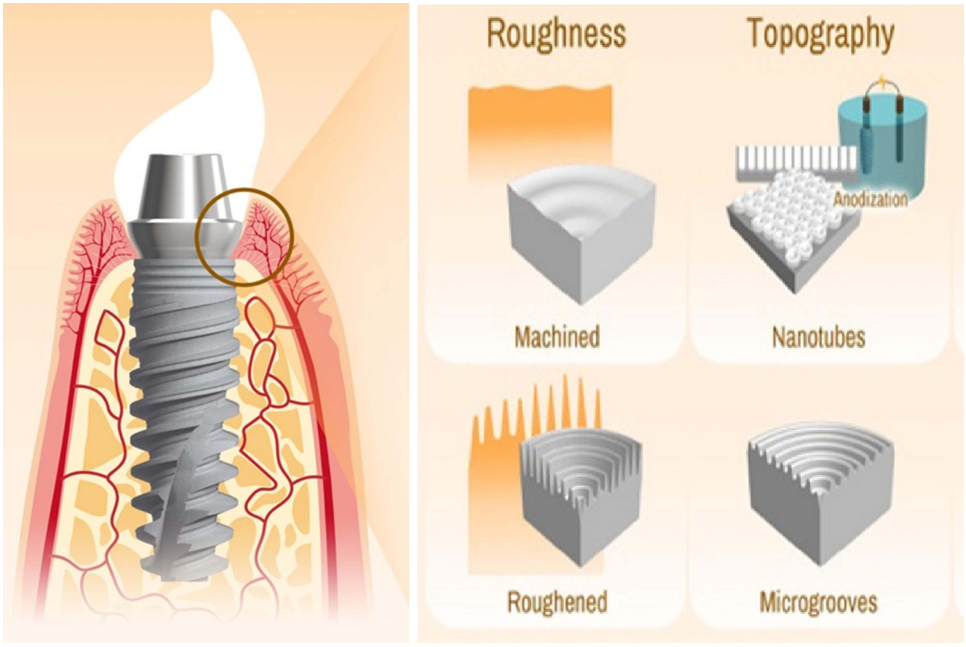

Figure 3 Schematic representation of surface modification using topography and roughness for the enhancement of per-implant soft tissue integration. Reprinted from *Int J Biol Macromol*, volume: 208, Deng Z, Liang J, Fang N, Li X. Integration of collagen fibers in connective tissue with dental implant in the transmucosal region. 833–843, Copyright 2022, with permission from Elsevier.[61]

integration. These include alternation of surface topography and material chemistry, biomolecular coating as well as structure design.[22] Particularly, the notion of surface modification of implants has captured the interests of biomedical researchers and clinical scientists because the reactions of tissue and cells to the surface and the subsequent foreign body reaction depend on the surface properties of biomedical implants (Figure 3). This, in turn, governs the healing mechanism of permucosal implants and lowers the failure rate of dental implants by promoting osseointegration, controlling immune reactions, and the reduction of infection.[98,99]

The presence of organized nanostructures on the surface of dental implants can positively affect soft tissue–cell interactions.[100] The patterning can lead to peri-implant sealing through two routes: surface roughness by which the horizontal expansion of soft tissue is facilitated and surface hydrophilicity which changes the attachment behavior of peri-implant tissue to the implant.[101] As an example, Chen et al reported an enhanced peri-implant soft tissue sealing with an anodized Ti implant which was significantly higher than that of a non-anodized one after transcutaneous implantation in goat tibia for 8 weeks.[102] In addition, the soft tissue inserted into the nanopores was an indication of biological integration at the transmucosal region of the Ti implant. Gulati et al reported the promotion of alignment in gingival fibroblast cells due to the presence of organized TiO_2 nanotubes which led to enhanced cell adhesion and migration (Figure 4A and B).[103]

Miao et al also reported an improved attachment of human gingival fibroblast and human gingival epithelial cells to Ti with micro- and nano topography compared to that of smooth Ti which indicated epithelial sealing.[104] Nothdurft et al have shown different surface responses of epithelial cells and fibroblasts on Ti substrate which was related to different surface topography.[105] Their findings showed a higher fibroblast cell adhesion on machined and polished surfaces than sandblasted substrate due to surface roughness but not for epithelial cells. Kato et al have shown an increased gingival fibroblast cell in the alkali-heat treated Ti implant and found a perpendicular attachment of collagen fibers to implant around rabbit mucosa after 8 weeks of implantation at the hard palatal plate (Figure 5a–f).[106] This finding indicated a direct metal-fiber integration in the connective tissue layer. Further, the nanomodification of Ti dental implants and abutments in the canine revealed soft tissue integration abutment after 12 weeks of healing.[107]

The surface topography not only can guide the synthesis and secretion of collagen fibers but also guide the orientation of fibers and fibroblast behavior. There is increasing evidence demonstrating the potential surface topography on the orientation of fibroblast adhesion and fiber orientation.[103,108] For instance, Liu et al have reported that the presence of titanium nanotube produced by anodization positively affected the attachment and spreading behavior of human gingival fibroblast and promoted the secretion of collagen type I.[109] In another study, Nevins et al have shown the guidance of collagen fiber in a perpendicular fashion which was induced by laser-ablated microgrooves.[110] In a study, Wang et al aimed to assess the soft tissue healing Ti abutment with surface nanotopography. Their findings showed that Ti-based abutment anodized with nanotube and screwed to the implants increased connective tissue length and perpendicular collagen fibers in beagle dog when compared to machined abutment[111] (Figure 6).

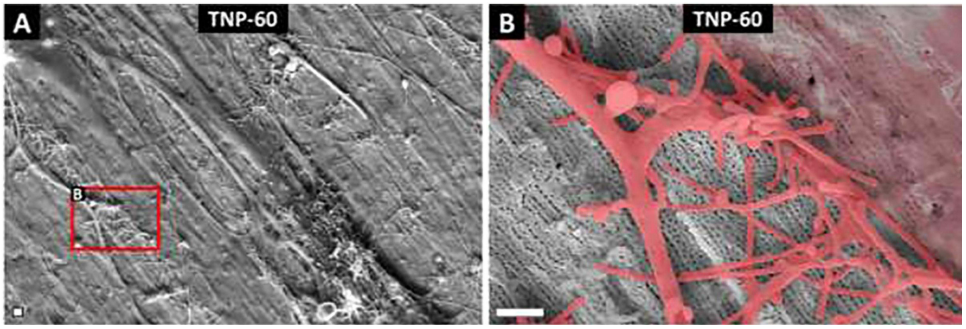

Figure 4 SEM images of (**A**) extensions of filopodia and parallel alignment of fibroblasts on the nanoporous substrate after 7 days of cell culture and (**B**) Higher magnification of the marked area in (**A**). The filopodia are shown in red color. Reprinted from Mater Sci Eng C, volume 112, Gulati K, Moon H-J, Kumar PTS, Han P, Ivanovski S. Anodized anisotropic titanium surfaces for enhanced guidance of gingival fibroblasts. 110860, Copyright 2020, with permission from Elsevier.[103]

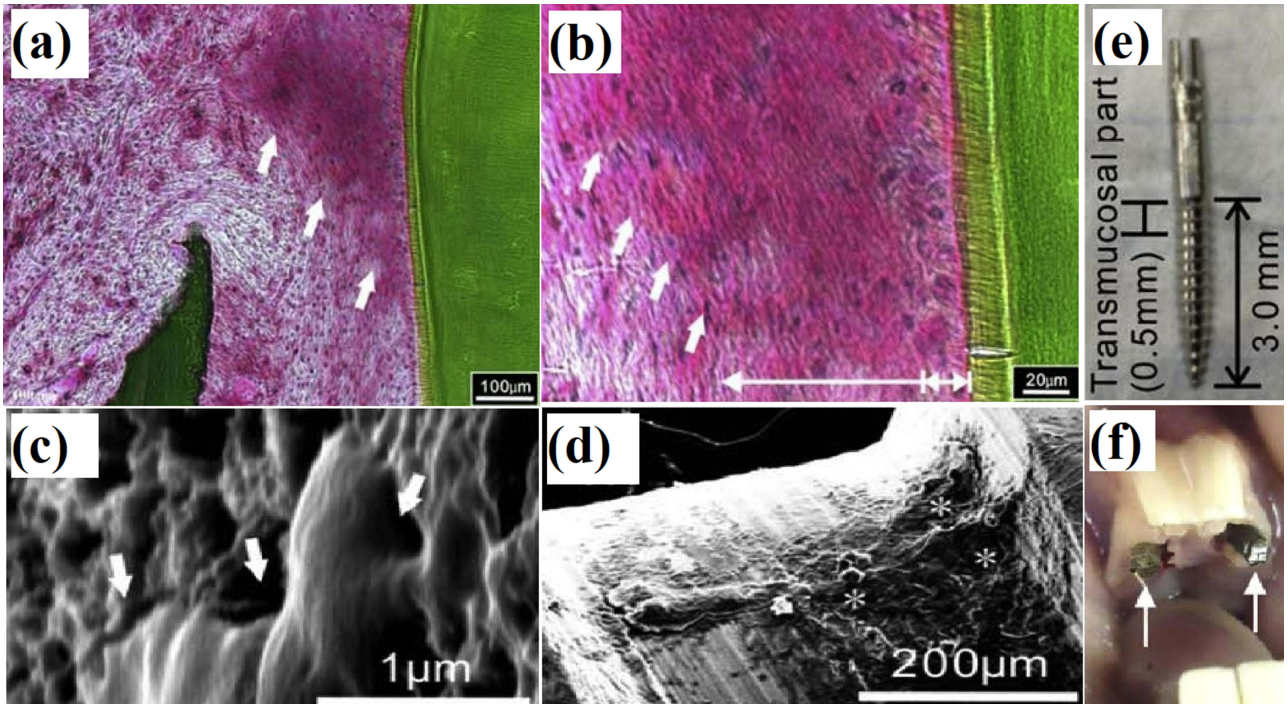

Figure 5 Effect of surface nanotopography on soft tissue integration (**a** and **b**) Villanueva–Goldner staining of peri-implant tissue around titanium implants; collagen network at the connective tissue region periodontal tissue comprised of and cell-rich later on the cementum (double-headed white arrows) and the dentogingival fiber (single-head white arrow), (**c**) wavy form attached tissues which was terminated into nanopores (single head white arrow) (**d**) abundant tissue attached at the transmucosal aspect of dental implant with nano topography (white asterisk), (**e**) mini Ti implant, (**f**) placement of mini Ti implant into the palatal of rabbit. The white arrows show the implant which is a bilaterally placed into the hard palatal plate in which the coronal part of the implant threading contacts the surface of gingival tissue. Reprinted from *Dent Mater*, volume: 31(5), Kato E, Sakurai K, Yamada M. Periodontal-like gingival connective tissue attachment on titanium surface with nano-ordered spikes and pores created by alkali-heat treatment. e116–e130, Copyright 2015, with permission from Elsevier.[106]

Topography-mediated Antibacterial Performance

The successful clinical performance of an implant is highly dependent on the key constituents of biological organisms such as bacteria, cells, etc. This is holistically defined as biocompatibility which is directed by properties such as surface topography. When a medical implant such as Ti is indwelled in the body, it will be in immediate contact, with complex host body fluids depending on the implantation site.[112] The dental implants are exposed to both serum and saliva encountered in the oral cavity. Because they are intrinsically foreign bodies, they are sensitive to the formation of biofilm which triggers inflammatory reactions and provides an ideal substrate for the adhesion of bacterial cells.

The interaction between the surface of the implant and the pathogenic oral biofilm that is formed around the implant can cause an exacerbated immunogenic response, and in turn, peri-implant disease.[113] If this biofilm accumulation is not properly controlled, then their colonization of the mucosa causes peri-implant mucositis.[114] Importantly, plasma proteins and salivary immediately coat the surface of the dental implant and this enables the adherence of oral microorganisms to the receptors in plasma and salivary and initiates microbial accumulation.[115] The intricate architecture of biofilm and the complex rough geometry of dental implants make this more challenging. To tackle these complications, the surface modulation of surface properties of dental implants has been suggested to reduce the release of metallic ions and the formation of biofilm.[116,117]

As Ti alloys have been extensively investigated as dental and orthopedic implants, the studies have mostly focused on the surface engineering of Ti implants to endow implant antibacterial properties.[118] This can be attained by precise control over the surface topography at the nanoscale. For instance, the bacterial adhesion on the implant surface on the nanoscale (10–100 nm) was found to be gradually prevented,[119] while bacterial adhesion on the microscale was shown to increase with surface roughness. This question of how the surface topography at the nanoscale can affect the colonization of bacteria is not yet fully understood. However, a possible mechanism was suggested as follows. The nanostructured surface topographies which are highly dense with a high aspect ratio can induce physical rupture in bacterial cells via

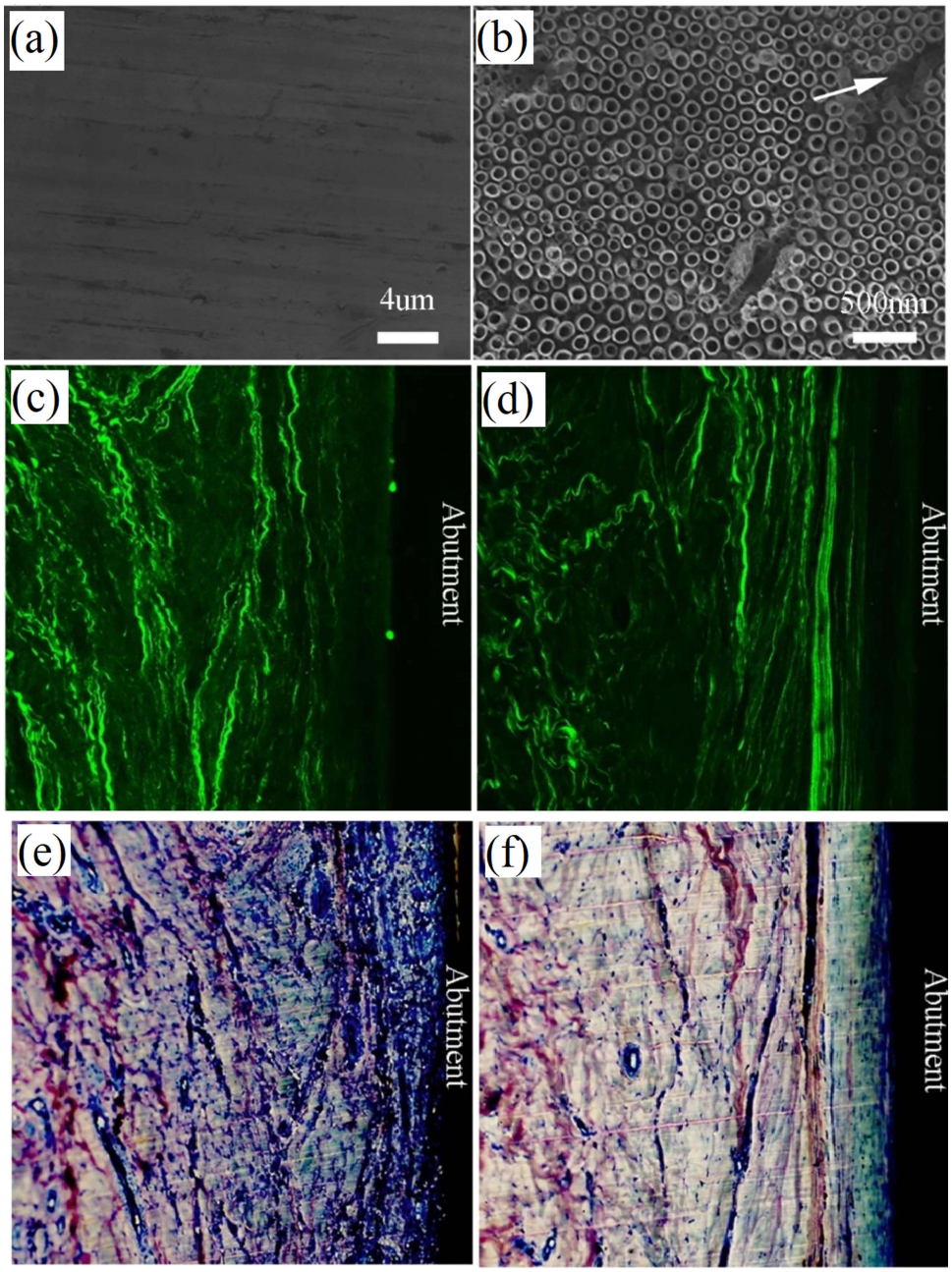

Figure 6 Surface observation of Ti abutments: (**a** and **b**) SEM images of machined surface and surface with nanotubular topography; white arrow indicates the shorter nanotubes which were formed in β-phase (**c** and **d**) Second harmonic generation (SHG) images of surfaces, (**e** and **f**) Histological images of machined and anodized nanotubular surfaces after 4 weeks of healing. The formation of less fiber composition and loose structure around machined abutment compared to more dense collagen fibers on nanotopographic abutment is clear and the orientation of collagen fibers is parallel to the abutment surface. Adapted from *BMC Oral Health*, volume: 23(1), Wang C, Wang X, Lu R, Cao X, Yuan D, Chen S. Influence of surface nanotopography and wettability on early phases of peri-implant soft tissue healing: an in-vivo study in dogs. 651, Copyright 2023, Creative Commons.[111]

mechanical force which leads to bacterial death and reduces biofilm formation.[120] In other words, the bacterial membrane cannot be easily stretched and spread on the surface with nanofeatures (eg, nanospears) causing perforation of the bacterial cell.[119,121] For example, Chopra et al have shown that nanopillar-like topographies including spinules, daggers, papillae, spikes, and flame could induce stretching in the bacterial membrane through adhesion forces which led to bacterial cell death.[121] In addition, the spinules and spikes with smaller sharp tips improved the antibacterial efficiency by the application of pressure on the membrane. This finding indicated the key role of the sharpness of nanotopography in antibacterial properties. Hayles et al have applied acid-etching to induce nanostructure on the Ti dental implant which was inspired by a dragonfly wing (Figure 7a and b). The nanopillar inspired by the dragonfly wing was shown to kill the

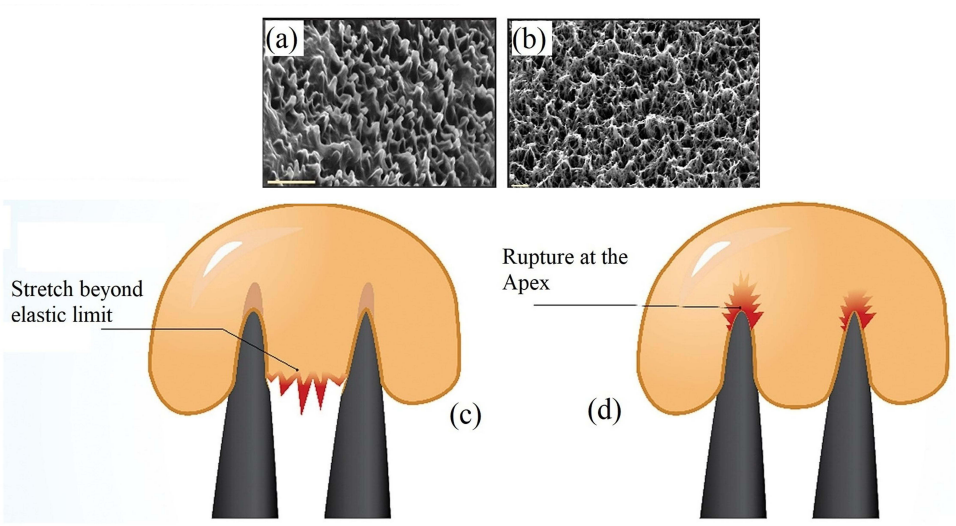

Figure 7 Dragonfly wing-inspired nanopillar prepared by acid-etching on Ti substrate: (**a** and **b**) Scanning electron Microscopic (SEM) images with scale bars of 1μm (**c** and **d**) Schematic representation of proposed antibacterial mechanism. Reprinted from *Mater Today Chem*, volume: 22, Hayles A, Hasan J, Bright R, et al. Hydrothermally etched titanium: a review on a promising mechano-bactericidal surface for implant applications. 100622, copyright 2021, with permission from Elsevier.[122]

bacteria by drawing it down along the nanostructure which causes lethal stretching of bacterial cell membrane between nanopillars (Figure 7c). In addition, the bacterial cell membrane is deformed and ruptured at the nanopillar apex (Figure 7d).[122]

Another possible mechanism for antibacterial effects due to surface nanotopography is the spatial confinement size effect which can provide conditions which are not suitable for the adherence of micro-sized bacteria.[123] This shows that modulating the topography to nanoscale can cause bacteria not to find suitable sites, leading to a decrease in adhesion to the surface. The efficiency of antibacterial surfaces relies on different parameters including dimensions, aspect ratio, as well as distribution.[119] For instance, Cao et al have shown reduced bacterial attachment and delayed the formation of biofilm by compassing the bacterial membrane with nanospears.[124] In another study, Gao et al have reported a reduction in bacterial attachment by nanospike topography.[125] In a study by Kunrath et al, a nanotextured Ti surface showed slightly higher antibacterial properties compared to that of a microtextured counterpart.[126] In contrast, the soft tissue around the dental implant was enhanced by nano texturization but had no remarkable antibacterial properties as Hall et al reported.[127] As can be observed from the above-mentioned results, nanostructures can be promising to protect the transmucosal region from bacterial invasion which can lead to enhancement in peri-implant tissue integration. Nonetheless, these findings are yet to be proved using animal models and clinical investigations.

The surface roughness which is a measure of surface irregularities can have a significant effect on the biofilm formation and microbial adhesion.[128] Moreover, it can increase osseointegration or bone-to-implant contact and further reduce the risk of implant failure.[31] It was found that the contact area for bacterial colonization is increased by increasing the surface roughness compared to a flat surface.[129] This facilitates and accelerates the maturation of biofilm on the surface of dental implants.[130] In this sense, Al-Ahmad et al have examined the in vivo bacterial adhesion on the TiUnite with the highest surface roughness showed the highest bacterial adhesion. This was attributed to the increased contact area for bacterial colonization compared to a flat surface.[129] This facilitates and accelerates the maturation of biofilm on the surface of dental implants.[130] Li et al recommended a surface roughness of Ra <0.4 μm for Ti dental implant.[131] In addition, Bollen et al have reported that the roughness value below 0.2 μm does not provoke plaque formation.[132] Nonetheless, the topography profile of dental implants allows for various patterns of bacterial cell adhesion and colonization which rely on its nanometric scale.[133]

Topography-mediated Immunomodulation

The surface topography which is highly related to surface roughness has been well documented to tune the immune cell response.[134–136] This capability to adjust the response of immune cells can lead to better soft tissue integration through

enhancing the adhesion and proliferation of epithelial and fibroblast cells.[137] Thus, switching of peri-implant macrophage phenotype from M1 (pro-inflammatory) to M2 (anti-inflammatory) be utilized as an immunomodulatory-based strategy to yield an appropriate immune microenvironment (Figure 8).[138,139]

A study by Ma et al has shown that the nanoscale topography of Ti implants can directly regulate the polarization of macrophages in which the surface with 30 nm nanoscale significantly improved M2 macrophage polarization and inhibited the inflammatory response than 80 nm in vitro and in vivo.[140] In addition, the macrophage shapes were found to be spindle-like and oval on the implant surface with 80 nm and 30 nm, respectively. This indicated that the nanotube diameter could play a key role in determining the morphology and behavior of macrophages.[141] In another study, the TiO_2 nanotube with a diameter of 30 nm induced M2 macrophage phenotype compared to that of 80–100 nm which induced M1 macrophage phenotype in vivo.[142] Similarly, the TiO_2 nanotube with a nanoscale diameter of 30 nm mediated M2c macrophage polarization compared to 80 nm which induced M1 macrophage polarization.[143] Ma et al have reported that the Ti implant with nanotubular arrays of 80 nm elicited an intense inflammatory response than that of 30 nm. In addition, an unstable balance of osteogenesis/osteoclasia around the Ti implant with nanotubular arrays of 80 nm was found with a bias towards osteoclasia. This was attributed to the direct role of nanotopography of the surface together with the promotion of secreted immune factors from cultured cells. This finding suggested that the alternation in the nanotopography of the Ti implant surface can not only control the polarization of macrophage but also manipulate the balance of osteogenesis/osteoclasia which enhances the clinical performance of endosseous implants.[144]

As discussed earlier, surface nanotopography plays an important role in inflammatory reactions and the modulation of macrophage phenotype. Studies have been conducted to understand the underlying mechanism that drives the attenuation of inflammatory responses. For instance, Zhu et al have found that the surface topography of TiO_2 honeycomb can be sensed by macrophages in different scales and the activation of the RhoA/ROCK signaling pathway shifted the macrophage towards M2 phenotype.[145] In another study, Neacsu et al reported that the suppression of MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) cell signaling pathways is the underlying mechanism by which the macrophage inflammatory response is attenuated.[146] Qi et al created the TiO_2 with a size of 30 nm adapted to protein ligands and found a remarkable attenuation of inflammatory macrophage polarization in vivo due to the inhibition of inflammatory nuclear factor kappa B (NF-*k*B) signaling pathway through activation of integrin-mediated focal adhesion kinase (FAK)-phosphatidylinositol-3 kinase γ (PI3Kγ) pathway.[147] This showed the effect of nanostructures on macrophage activation in proteins (Figure 9).

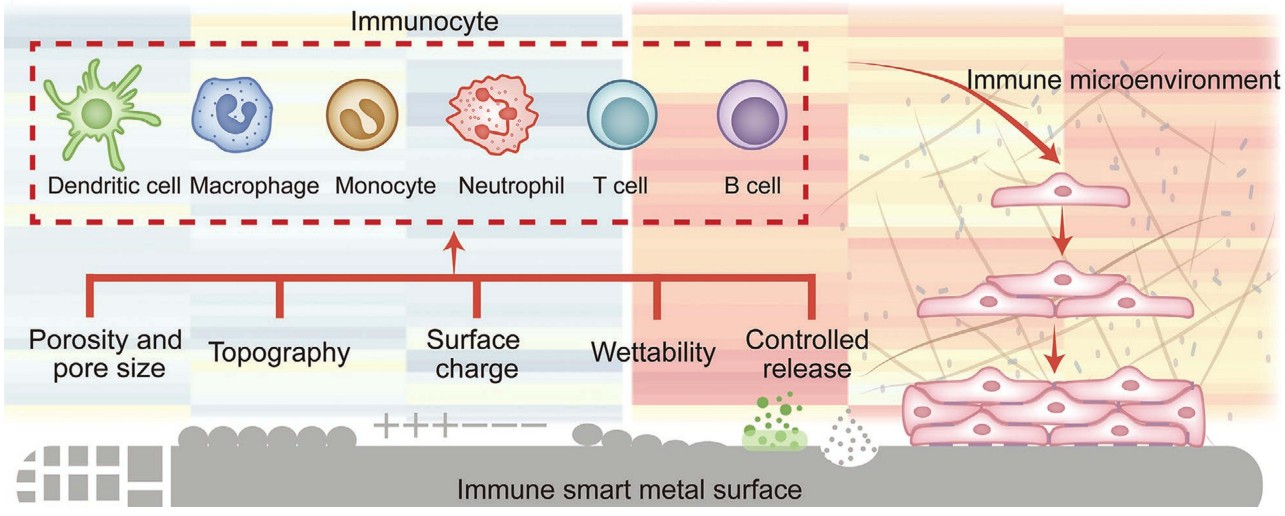

Figure 8 A schematic representation of immunomodulatory-based strategy. The modulation of immune cells towards the proper immune microenvironment surrounding the biomedical implant via tunning the properties of the implant. Reprinted from Liu R, Chen S, Huang P, et al. Immunomodulation-based strategy for improving soft tissue and metal implant integration and its implications in the development of metal soft tissue materials. *Adv Funct Mater.* 2020;30(21):1910672. © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[65]

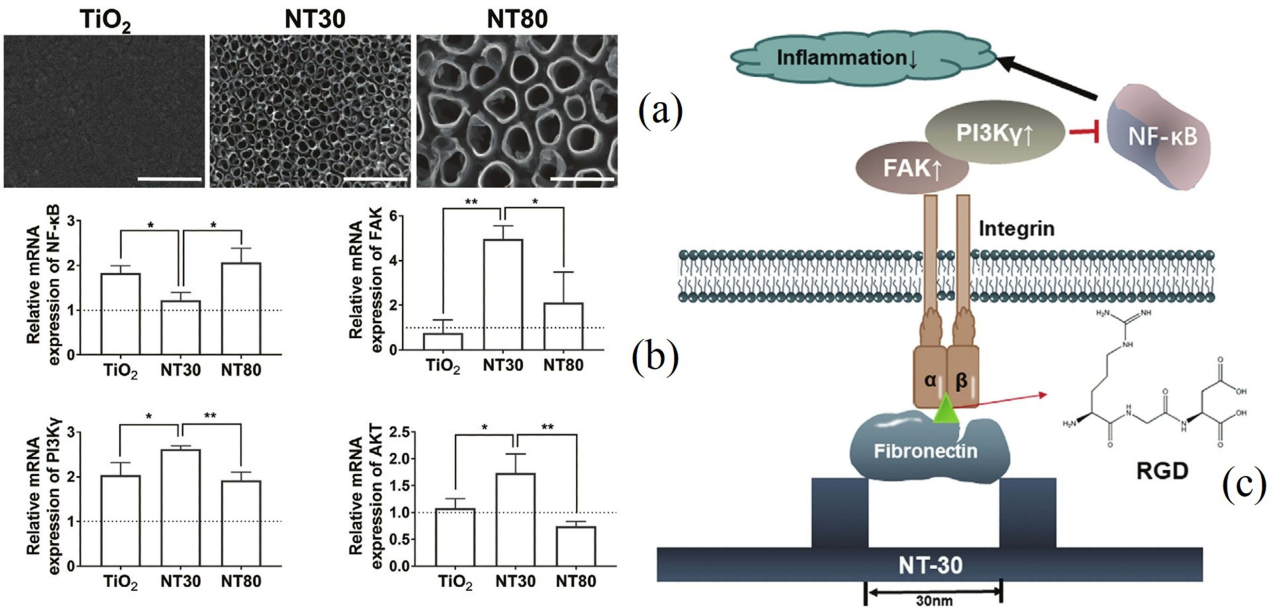

Figure 9 Effect of TiO_2 nanotube on macrophage activation (**a**) SEM micrographs of the anodically oxidized surface with a scale bar of 200 nm (**b**) the relative expression of mRNA of FAK, PI3Kγ, AKT, and NF-kB mRNA in cells with different surfaces; the dashed lines indicate the control data and asterisks denote statistically significant (*Significant p^* < 0.033 and **p < 0.002, **Very significant) (**c**) schematic representation of nanostructured effect on fibronectin-induced macrophage inflammation. Reprinted from Qi H, Shi M, Ni Y, et al. Size-confined effects of nanostructures on fibronectin-induced macrophage inflammation on titanium implants. *Adv Healthcare Mater.* 2021;10(20):2100994. © 2021 Wiley-VCH GmbH.[147]

Nanotopography-based Drug Delivery Systems

The increasing demand for specific treatments for patients seeking dental treatment led to several basic investigations on biomaterials with specific surface properties.[3] In this regard, biomaterial researchers and companies aim to develop implants with multifunctional surfaces that promote faster healing, downregulate the inflammatory response, and provide effective antibacterial properties.[31,148]

As already mentioned in Clinical Challenge of Ti-Based Implant, the adhesion of bacterial cells to the implant surface forms biofilm which causes local infection and triggers an inflammatory response, and consequently leads to the early loss of dental implant.[39,149] Thus, the production of dental implants capable of releasing antibiotics is desired. For this purpose, drug delivery systems can be used to functionalize the implant surfaces to tackle implant-related infections and reduce inflammatory responses.[27] In this regard, the nanostructured surfaces can act as drug-delivery systems for oral rehabilitation in which various biomolecules such as growth factors, and antibacterial and anti-inflammatory agents can be incorporated into their nanostructures.[150,151] For the loading of molecules to the surface of a dental implant, specific sites such as the nanoporous or nanotubes such as TiO_2 nanotubular are required.[27,152,153] In a study, Kunrath et al developed nanotopography of Ti dental implants by anodization followed by plasma surface treatment. Then, the surface was functionalized with a rifampicin-loaded poly(lactide-co-glycolide) (PLGA) layer. Their findings showed that the addition of antibiotic-loaded polymeric coating on a nanotopographical modified surface (TiO_2 nanotube) significantly inhibited Staphylococcus epidermidis (*S. epidermidis)* activity compared to machined and acid-etched Ti surface.[154] In another study, Kazek-kesik et al coated an amoxicillin-loaded PLGA on the anodized Ti implant.[155] Their findings showed a satisfactory antibacterial effect against Staphylococcus aureus (*S. aureus)* and *S. epidermidis*.

The incorporation of metallic nanoparticles into the nanostructured surface is another method of creating a drug delivery system aiming to enhance the antibacterial and antifungal properties in implant dentistry.[156–160] In a study, Gao et al applied a silver-embedded TiO_2 nanotube array to the surface of the Ti implant and their findings revealed an effective antibacterial activity against *S.aureus* for silver-containing nanotubular topography. This antibacterial activity was due to direct contact between the bacterial cells and the silver layer which damaged their cell walls.[161] In addition, the Ti implant with silver-containing nanotubular topography mitigated the inflammatory response in vivo which led to a significant decrease in the formation of a fibrous encapsulation in soft tissue peri-implant in vivo. Roguska et al have

embedded zinc and silver nanoparticles into the TiO_2 nanotubular arrays and their results revealed a distinct enhancement in the antifungal properties against Candida albicans (*C. albicans*) and Candida parapsilosis (*C. parapsilosis)* yeasts and antibacterial properties against *Streptococcus mutans* (*S. mutans*).[162] These synergistic antifungal and antibacterial properties are important in designing dental implants because of the co-existence of microorganisms in the biofilm and their colonization on the surface of the tooth causes dental caries and is responsible for dental failure.

Ethical Matters in Animal Studies

To make innovative dental implants available to the market and patients, thorough pre-clinical and clinical studies need to be conducted. For the implantable materials, in vitro cell cultures such as ISO-10993 and in vivo animal studies are usually used. Numerous in vitro studies have elucidated the effect of biomaterial surface properties on bacterial responses that are involved in clinical applications; however, they cannot represent the complex healing process in periodontal tissue. Moreover, the dynamic microenvironment in oral diseases such as periodontitis cannot be explored by in vitro models due to their inability to reproduce the systemic response in humans.[163] In contrast, the in vivo models using large animals (eg, dogs, pigs) can simulate oral environments and periodontal conditions more similar to humans. In addition, they offer closer metabolism speed to humans but are not completely comparable to humans. Therefore, in vivo studies play a key role in the successful translation of dental implants into the market. Nonetheless, the ethical approval and number of animals may be challenging. The ethical issues regarding the experiments using animals started in 1959 and emphasized the reduction, refinement, and replacement of animal use.[164]

According to this principle, the numbers of animals for the scientific experiment need to be reduced. Besides, the distress and pain in animals need to be minimized during experiments. Although this is the cornerstone of animal experimentation, nonetheless, there are questions about the implementation of this regulation.[165] Large (dogs, pigs) and small animal (rats, rabbits, mice) models have been traditionally utilized in dental-related experimentations.[166] Based on the literature, small animal models have been dominated in biomaterial research. This is due to their cost-effectiveness in which limited implant samples with an appropriate size to small surgical sites need to be fabricated in the laboratories.[167] In contrast, large animal models are costly due to the requirements for high feeding costs, extra housing, complex ethical issues, and post-operative care.[168] For this reason, the in vivo experiment should be carefully designed based on the proximity to human physiology, immunological features as well as the number of animals.[169] A summary of in vitro and in vivo tests and their corresponding ethical approval for Ti dental implant surface nanotopography is shown in Table 1.

Table 1 A Summary of in vitro and in vivo Tests and Their Corresponding Ethical Approval for Ti Dental Implant Surface Nanotopography

Source	Testing	Ethical Approval	Reference
Molar teeth of adults (Healthy human gingival tissues)	In vitro	Independent Ethics Committee of Shanghai Ninth People's Hospital	[104]
Canines	In vivo	Institutional Animal Care and Use Committee of the University of Texas Health Science Center at San Antonio (UTHSCSA)	[107]
Sprague-Dawley rats (Fibroblasts)	In vitro	Animal Research Committee of Tokyo Dental College (Protocol No. 232,604)	[106]
Japanese white rabbit	In vivo	Animal Research Committee of Tokyo Dental College (Protocol No. 252,602)	[106]
Male beagles	In vivo	Animal Ethical and Welfare Committee of the Beijing Stomatological Hospital, Ref. KQYY-201909-005)	[111]
Redundant alveolar bone from healthy patients (Fibroblast extraction)	In vitro	University of Queensland Human Research Ethics Committee (Approval number: 2019 000 134)	[121]

(*Continued*)

Table 1 (Continued).

Source	Testing	Ethical Approval	Reference
Healthy individuals with no clinical periodontal attachment or bone loss (Saliva extraction)	In vitro	The University of Queensland, institutional human ethics committee, approval number: 2019 001 113)	[121]
Rats	In vivo	Animal Experiment Ethics Committee of the Fourth Military Medical University	[144]
Healthy donors after maxillary third molar extraction (BMSC separation)	In vitro	The medical ethics committee of the School of Stomatology of the Fourth Military Medical University	[144]
Male wild-type (WT) mice male Cre*RBP-Jfl/fl (knockout [KO]) mice	In vivo	The University Research Ethics Committee of The Fourth Military Medical University.	[142]
Male Sprague Dawley rats	In vivo	The animal experiment ethics committee of the Fourth Military Medical University	[140]
Healthy After maxillary third molar extraction (BMSC extraction)	In vitro	The medical ethics committee of the School of Stomatology of the Fourth Military Medical University	[140]
Male Sprague Dawley rats	In vivo	The Animal Experiment Ethics Committee of the Fourth Military Medical University (No. KY20194055)	[161]
Lewis rats (adipose tissue-derived mesenchymal stem cells (ASCs))	In vitro	Institutional Animal Ethics Committee (Protocol No. 7467)	[154]
Kunming mice	In vivo	The Committee for Animal Research of the School of Stomatology, Wuhan University, China (Protocol number 69/2017)	[147]
-	-	The Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS.REC.1401.084)	This study

Regulatory Hurdles and Commercialization

The success of topographically surface-engineered Ti-based dental implants to date is restricted to clinical studies and is not completely present in the clinical market and needs progress to achieve clinical patients. Therefore, academic, industrial, and clinical researchers should actively seek more generalized data. For this purpose, some challenges need to be overcome. The first challenge is the long-term release of Ti particles around the dental implant that may influence the progression of per-implant disease due to the foreign body response or alternations in the oral microbiome.[170] This may be due to the release of fragments resulting from delamination or breakage of the dental implant. This reveals the important role of mechanical stability of dental implants. The nanostructuration of Ti-based implants has been found to modify their mechanical properties. Thus, the Ti dental implant with a nanostructured surface should possess sufficient mechanical stability to prevent any delamination during the insertion of the implant.[171]

The second key issue in the translation of topographically surface-engineered Ti-based dental implants in the market is the dearth of information on sterilization protocols.[172] This is important in clinical application in patients as it may prevent possible contamination and wrong interpretation of outcomes in humans. Besides, the dental implants will not receive approval from the responsible agencies if there is a lack of a precise and safe protocol for sterilization. Most of the published studies slightly discuss the sterilization process to date. Thus, the protocols for sterilization need to be described in study methodologies and presented with a comparative analysis before and after the given sterilization process. The commonly suggested sterilization for metallic biomaterials in the literature includes autoclaves, heating systems, UV light, ethylene oxide, and gamma irradiation.[173,174] However, these sterilization processes may alter the physical and chemical properties. The study published by Guo et al corroborated that both wet and dry autoclave sterilization compromised the topography of TiO_2 nanotube fabricated by anodization.[175]

The third issue is the biological response of Ti dental implants. After the development of nanotopographically modified Ti dental implants, their biological responses and cellular mechanisms should be investigated before their translation into the market. Although the effect of specific material properties such as surface topography on the adhesion and proliferation of relevant cells can be evaluated by easy and cost-effective in vitro models compared with in vivo models, however, the complexity of the physiological microenvironment cannot be reflected by such setup. Therefore,

a reliable in vitro test system capable of yielding highly reproducible outcomes concerning the biological response of patients after implantation of dental implant.[176] An alternative biomimetic in vitro testing mimicking human intra-oral hard and soft tissue wound niche has been used to evaluate the performance of acid-etched dental implants.[177]

The final step in the translation of topographically surface-engineered Ti-based dental implants into the market is to receive regulatory approvals as the last roadblock before their commercialization. For this purpose, more pre-clinical studies on animal models need to be carried out which is then validated in human clinical trials.[178] The national regulatory agencies in different countries approve pre-clinical studies according to their existing guidelines. Therefore, they have their timeframes required for the approval. In addition, international accreditation organizations such as the Food and Drug Administration (FDA) and Conformite Europeene (CE) need remarkable time for the commercialization of medical implants before their marketing. To address this, the industrial communities mentioned in the Table should be actively engaged with regulatory agencies and have an understanding of regulatory hurdles during the development of the next generation of dental implants.

In light of this, the role of global interdisciplinary research programs in collaborating with academic researchers, industrial professionals, and clinicians is undeniable which further leads to the facilitation of smart Ti dental implant translation. A summary of ongoing or completed Ti dental implants on the peri-implant soft tissue integration and reaction is shown in Tables 2 and 3.

Future Perspective

Additive Manufacturing

The recent progress in materials science engineering, nanotechnology, and additive manufacturing techniques offers new opportunities, and this groundbreaking technique is expected to remarkably affect the medical implant industry and drive conventional implant manufacturers to engage and adapt such advancement in enhancing their existing technology and designing a new generation of smart implants. In this regard, the combination of additive manufacturing (AM) technology with surface engineering and nanotechnology-assisted functionalization towards the development of the new generation of smart medical implants in the coming years. The AM which is also termed as rapid prototyping refers to technologies that fabricate three-dimensional (3D) objects with precise and complex geometrical shapes via computer-

Table 2 Current Completed Clinical Trials on Ti Dental Implant Evaluating the Soft Tissue Integration and Response. Data Source: https://clinicaltrials.gov/

Clinicaltrials.gov Identifier	Study	Purpose	Treatment
NCT05843526	Effect of material component	Peri-implant soft tissue host response	Dental implant
NCT01961635	Effect on marginal bone	Soft tissue healing	Dental implant
NCT05805033	Influence of Material (roughness)	Peri-implant soft tissue integration	Dental implant
NCT04436939	The formation of plaque	Soft tissue response	Dental implant
NCT02159183	Implant with ESTA surface	Soft tissue reaction	Roxolid implant

Table 3 Current Completed Clinical Trials on Soft Tissue Healing Around Commercialized Ti Dental Implant. Data Source: https://Clinicaltrials.gov

Clinicaltrials.gov Identifier	Study	Purpose	Treatment
NCT04383834	Soft tissue thickness	Soft tissue stability and health	NobelActive TiUltra
NCT03582657	Effect of nanostructured	The rate of per-implantitis	KONTACT N
NCT03649100	Effect of nano-HA coating	Implant stability	Hiossen ET III
NCT00782171	Effect of surface roughness	Implant stability and performance	SLActive

aided design (CAD) software. In a recent report, a 3D printed Ti implant with nanostructured TNT with arrays of pillars and spikes was fabricated by the combination of 3D printing.[179]

The 3D-manufactured Ti implants are promising future trends in the medical industry as they enable the manufacturing of customized dental implants for clinicians in specific cases.[180,181] The combination of 3D manufacturing and topographical surface modification of dental implants may lead to the next generation of dental implants. However, it should be critically investigated by preclinical models before translation to clinical evaluations and later market.[182] Moreover, peri-implant inflammation frequently remains in patients with dental implants and these multifunctional implants may find a spot in clinical dentistry. Therefore, the future direction is to translate the preclinical research into commercialized (marketable) implants, while large productibility, cost-effectiveness, and durability need to be taken into account as key factors for their commercialization.

Machine Learning

Machine learning (ML) and artificial intelligence strategies have gained attention in the development of biomaterials.[183] For instance, AI approaches have been applied to nanoengineered Ti-based dental and orthopedic implants[184] enabling the identification of critical material-dependent parameters among reports. In various biomedical fields that are involved in the war against infection and immunomodulation, ML and AI strategies may be of great help in organizing abundant research and clinical data.[185,186] Thus, it is recommended to develop a publicly accessible online platform on which the outcomes of clinical studies associated with immunomodulation and antibacterial which is kept and supported by the National Institute of Health (NIH).

Conclusion

Currently, implant dentistry is used in replacing missing teeth in partial edentulous conditions. Nonetheless, their success is undermined due to bacterial infection and poor osteointegration which leads to implant failure. This means that the success of rehabilitation by using dental implants relies on both proper osseointegration and soft tissue integration in the absence of inflammatory response. The failure of dental implants due to peri-implantitis brings forth emotional, financial as well as technical burdens to patients and dentists. Therefore, the development of strategies for the treatment of peri-implant disease has been of great research interest. Furthermore, tissue regeneration is compromised by the excessive immune response around the dental implant, while the excessive suppression of immune response can lead to uncontrolled accumulation of pathogens and peri-implantitis. To address these issues related to conventional Ti dental implants, topographical surface engineering of dental implants has been reviewed in this paper to enhance the overall performance.

In the author's opinion, the topography engineering of Ti-based dental implants at the nanoscale possesses a positive regulatory effect on immune response and soft tissue integration and this plays a key role in the future of dental implants. The development of a dental implant with an immune-informed surface is desirable which secures the success rate of the dental implant, minimizes clinician visits, and decreases patient discomfort. In the present review, a summary of recent progress in understanding the role of surface topography of Ti implants in controlling and directing the immune response to improve soft tissue integration and prevent biofilm formation is provided. As discussed, the surface modification of Ti implant through topography in this study, revealed promising results in defending trans-mucosal region by endowing antibacterial properties and manipulation of macrophage behavior. Thus, it may reduce peri-implant infection and in turn, increase the survival rate of dental implants in clinical situations. However, long-term in vivo studies need to be conducted because the formation of soft tissue integration takes 6 to 8 weeks during which the post-surgical inflammation mediated by oral pathogens could compromise soft tissue integration.[60] Furthermore, the desired clinical performance of nanotopographically modified dental implants with immunomodulatory and antibacterial properties needs to be investigated in patients with compromised conditions such as diabetes and osteoporosis.[187]

Acknowledgment

Hossein Mohammadi and Mona Ebadi are the co-first authors of this study. Mona Ebadi and Hossein Mohammadi are the co-correspondence authors for this study.

Funding

This work was supported by Key Result Area (KRA-2023-001), Fundamental Research Grant Scheme (FRGS/1/2022/STG05/UKM/02/4), Research Council of Kermanshah University of Medical Sciences with grant no. 4010125, and Universiti Tenaga Nasional (UNITEN) with grant no. J510050002-IC-6 BOLDREFRESH2025-CENTRE OF EXCELLENCE.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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