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Topography-mediated immunomodulation in osseointegration; Ally or Enemy

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Abstract

Osteoimmunology is at full display during endosseous implant osseointegration. Bone formation, maintenance and resorption at the implant surface is a result of bidirectional and dynamic reciprocal communication between the bone and immune cells that extends beyond the well-defined osteoblast-osteoclast signaling. Implant surface topography informs adherent progenitor and immune cell function and their cross-talk to modulate the process of bone accrual. Integrating titanium surface engineering with the principles of immunology is utilized to harness the power of immune system to improve osseointegration in healthy and diseased microenvironments. This review summarizes current information regarding immune cell–titanium implant surface interactions and places these events in the context of surface-mediated immunomodulation and bone regeneration. A mechanistic approach is directed in demonstrating the central role of osteoimmunology in the process of osseointegration and exploring how regulation of immune cell function at the implant-bone interface may be used in future control of clinical therapies. The process of peri-implant bone loss is also informed by immunomodulation at the implant surface. How surface topography is exploited to prevent osteoclastogenesis is considered herein with respect to peri-implant inflammation, osteoclastic precursor-surface interactions, and the upstream/downstream effects of surface topography on immune and progenitor cell function.

Keywords

Immunoengineering; Implant surface topography; Roughness; Nano; Oncostatin M; BMP-2; Macrophage

1. Introduction

Endosseous implant success requires the life-long accrual and maintenance of bone at the alloplastic interface. Osseointegration was defined as “the direct structural and functional connection between the living bone and surface of a load-bearing implant” [1]. The definition implies that the bone tissue is formed against the endosseous implant surface and

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that it is maintained throughout the functional lifetime of the implant. At this interface, the biologic mechanisms affecting bone formation and remodeling are affected by the implant design, alloplastic surface characteristics, altered biomechanical environment, host status, surgical technique and loading conditions [2,3]. As such, the exact mechanisms underlying osseointegration and the causes of its failure remain incompletely defined. With expanding prescription of endosseous implants to include scenarios presenting higher risk local and systemic factors, there is a growing need for improving clinical control of the implant-bone interface and osseointegration.

Peri-implant bone formation occurs reproducibly by the proscribed surgical disruption of bone tissue and the insertion of an alloplastic surface into the bone and bone marrow. Inflammation is inherent to this process. While earlier studies focused on bone formation and the role of surface-adherent osteoprogenitor cells, continued investigations have expanded to include the role of osteoclasts in ongoing resorptive processes. After implant placement, the bone-implant interface is instantly filled with a fibrin coagulum enriched with growth factors and cytokines and containing platelets, erythrocytes, neutrophils, macrophages and debris of cortical and trabecular bone. These represent cells of the innate immune system and bring to light the previously overlooked roles of the immune cells in the control of interfacial bone accrual (net result of bone formation and bone resorption) and their interplay with bone forming and bone resorbing cells that define the osseous interface.

As originally conceived, the function of immune cells in bone biology was related to osteoclastogenesis [4], but many studies of bone formation and bone regeneration have revealed important regulatory functions of immune cells on the regulation of osteoblast function and bone regeneration [5–9]. The dental implant surface character (bulk chemistry, topography, hydrophilicity) alters the adherent cells phenotypes, and the interaction of immune cells with the endosseous implant surface can alter immune cell function, further underscoring the importance of osteoimmunology in the process of osseointegration.

Understanding how implant surface characteristics inform adherent immune cell function is a central aspect of understanding the process of bone accrual that results in osseointegration. This review summarizes what is known regarding immune cell–implant surface interactions and places these events in the context of bone regeneration and osseointegration. This effort demonstrates the central role of osteoimmunology in the process of osseointegration and explores how the regulation of immune cell function at the implant-bone interface may be used to control/manipulate clinical outcomes.

2. Osseointegration

2.1. Osseointegration defined as functional, histologic and molecular osseous processes

The central success for bone anchoring of titanium endosseous implants emerged from observations of the functional immobility of the implant being associated with the absence of infection, pain or other signs of failure. Both Branemark and Schroeder identified bone anchorage or ankylosis as a key to successful endosseous implant therapy [1,10]. In 1976, Kydd and Daly demonstrated that endosseous conical titanium alloy implants were immobile (resisted rotation) five months following surgery [11]. Branemark’s findings and

the ongoing development of ground section histology [12,13] resulted in associating this success with the formation of a ‘direct’ bone-to-implant interface lacking an intervening fibrous connective tissue ‘scar’. Thereafter, immobility of the endosseous implant was the central clinical determinant of functional success. Sennerby and Thomsen demonstrated that experimental inflammation resulted in impairment of osseointegration and was an early indication that inflammation was an important target for clinical endosseous implant success [14]. The conceptual evolution of osseointegration over time is depicted in Fig. 1.

2.2. Molecular and cellular processes of osseointegration

The complete molecular mechanism(s) of osseointegration and the cellular interactions that occur on the implant-bone interface and the surrounding tissue remain to be fully elucidated. These processes have been studied in human and animal models, and attempts have been made to correlate the molecular events and phenotypic observations with histologic representation of bone formation at the implant surface [15–26]. A number of key biological processes including inflammation, neurogenesis, angiogenesis, extracellular matrix (ECM) deposition and osteogenesis, as well as the associated signaling pathways are temporally regulated during osseointegration [15–17,27]. Gene expression events in the process of bone formation are recapitulated at the developing bone-implant interface [17,25].

Prominent up-regulation of neurogenesis related genes including those associated with neural tube, axon formation and neural signal transduction have been reported during osseointegration *in vivo* [17]. Both neurofilament-positive fibers and nerve bundles have been observed near the titanium implant surface [28,29]. These findings suggest that neurogenic tissues are regenerated during endosseous implant osseointegration. In addition, nervous system-related genes may play an active role during bone regeneration. As an example, neuropeptide Y, a nervous system-related gene, has been shown to modulate osteoblast function *in vivo* [30,31]. Neurotrophic factors such as BDNF produced by peripheral nerve injury can promote osteogenesis *in vivo* [32]. NGF that is upregulated in macrophages and mesenchymal stem cells (MSCs) during osseous regeneration may be a therapeutic target for enhanced osseointegration [33]. More general studies of regeneration underscore the role of innervation in regeneration. While studies of bone regeneration implicate neurogenesis in successful repair, the complex interactions of MSCs, nerve cells and immune cells remain to be elucidated [34].

Peri-implant angiogenesis is induced by vascular endothelial growth factor (VEGF), basic fibroblast growth factor, angiopoietin 1, platelet derived growth factor (PDGF), insulin-like growth factor (IGF), and hypoxia-inducible transcription factor expressed by implant adherent cells [26,35]. Angiogenesis is modulated in implant surface-topography dependent ways [36] and VEGF signaling has been defined *in vivo* to promote bone formation at the implant surface [37]. There is a general understanding of VEGF’s role in bone repair [38] and more complex regulation is suggested. For example, osteoprogenitor cell-secreted VEGF recruited both MSCs and macrophages to bone defects that ultimately modulated proinflammatory cytokine expression and increased bone formation *in vivo* [39]. These types of indirect effects (cell-cell interactions) on osseointegration may be influenced by

implant surface topography and further control osteogenic and inflammatory events in promoting osseointegration.

Osteoinduction and differentiation of stem cells into osteoprogenitor cells on the implant surface are regulated by key transcriptional regulators including Runt-related transcription factor 2 (Runx2) and Osterix [40]. Osteogenesis on the implant surface is indicated by the expression of alkaline phosphatase (ALP), integrin-binding sialoprotein (BSP), osteopontin (OPN), osteonectin (ON), osteocalcin (OC). The presence of these bone components at the interface was affirmed histologically [41]. The process is affected by several growth and differentiation factors including those of the bone morphogenic protein (BMP) and transforming growth factor (TGF) family.

Extracellular matrix components expressed at the forming interface comprise type 1 collagen, vinculin, fibronectin, and various proteoglycans including Decorin and Biglycan [21,26,42,43]. Immunomodulatory control of ECM formation is well defined in terms of biologic processes [44]. Examples of inflammatory cell or inflammatory mediator changes in ECM production affecting bone repair *in vivo* exist, and this occurs at the local level and by influence of systemic inflammation [45,46]. How immune cells and inflammatory mediators are temporally regulated at the implant surface to influence these first impactful stages of ECM formation during osseointegration have not been mechanistically explored. The potential complexity of this regulatory relationship is further influenced by our growing knowledge of the impact of ECM physical properties on immune cells (and MSCs) function [47]. The implant surface represents an infinitely stiff surface, yet how topography influences the stiffness of the superimposed forming and immature bone matrix and its downstream effects on cell function are not known.

Ultimately, inflammation-mediated changes in ECM production occur through transcriptional regulation as well as post-transcriptional modification involving cross-linking and protease activity. Prominent changes in immunomodulatory gene expression within ECM forming MSCs include both the NF-κB and NLRP3 pathways. The early immunoinflammatory changes appear to be regulated via the I-κB kinase/NF-κB cascade, whereas the later osteogenesis-related mechanisms are regulated by TGF-β/BMP, Notch and Wnt signaling as shown in a transcriptional profiling of osseointegration in humans [17]. Multiple studies have demonstrated that the expression of these factors and proteins may be altered by implant surface topography as discussed below.

2.3. Effect of implant topography on osteogenic molecular and cellular processes

Creating a favorable extracellular microenvironment to trigger the migration and adhesion of MSCs on the implant surface and the subsequent differentiation of MSCs into osteoblasts is important. How MSCs and osteoprogenitor cells perceive the surrounding microenvironmental cues has been an area of active research [48–60]. The endosseous implant surface is an essential environmental factor affecting this phenomenon.

Specific surface topographic dimensional parameters have been defined and the relative effects of smooth (0.0–0.4 μm S(a)), minimally rough (0.5–1.0 μm S(a)), moderately rough (1.0–2.0 μm S(a)) and rough (>20.0 μm S(a)) surface topographies on the resulting bone

to implant contact were identified [61–63]. In addition, different nanomodifications have been applied to implant surfaces, either directly on machined surfaces or by overlaying nanofeatures on microstructured topographies. The specific dimension and attributes of the nano-structures promote different outcomes compared to smooth or micron-scale surface modifications both *in vitro* and *in vivo* [64,65]. The current literature supports the hypothesis that titanium surfaces which mimic the physical properties of osteoclast resorption pits created during normal bone remodeling, such as roughness and complex hierarchical submicron and nanoscale structures, appear more effective in supporting osteoblast differentiation *in vitro* and osteogenesis *in vivo* [64–67] (Fig. 2).

Multiple levels of data indicate that implant surface topography directly modulates osseointegration by influencing the osteoinductive and osteogenic activities of implant adherent MSCs or osteoprogenitor cells [68–74]. The physiological, cellular or molecular events – i.e. the mechanisms – acting at implants with altered surface topography to promote this surface-directed increase in bone formation and its accrual were elucidated by Boyan and coworkers (reviewed in Refs. [75,76]). It was demonstrated that osteogenic proteins and osteoinductive cytokine production in implant adherent cells, osteoblastic and osteoprogenitor cells (most notably MSCs), increase with respect to micron scale surface topography modification *in vitro* [24,75,76]. Other *in vitro* and *in vivo* studies that focused on the impact of enhanced surface topography on osteoinductive transcription factors demonstrated that it increases the expression and activity of both Runx2 and Osterix within implant adherent cells [40,77,78]. Topographic enhancement of the titanium surface also accentuates BMP mediated signaling in implant adherent osteoblastic cells *in vitro* [79,80].

Many microRNAs influence these key osteoinductive pathways in implant-adherent or adjacent cells, and implant surface character has been shown to regulate these microRNAs [81]. Exosomes have microRNA cargo [82–87], and are secreted by implant adherent cells as a communication mechanism. Micro/nano-textured hierarchical titanium topography was shown to induce osteogenesis *in vitro* and improve osseointegration *in vivo* by promoting osteoinductive exosome biogenesis and secretion in MSCs [88]. In addition, titanium surface characteristics influence DNA damage and the DNA repair pathway, including epigenetic factors, in MSCs and osteoblasts both *in vitro* and *in vivo* [89, 90]. The superior osteogenic potential of the rough surfaces was attributed to their different epigenetic landscape, and specifically the DNA methylation [90–92].

Further *in vitro* and *in vivo* studies have investigated the various mechanisms of cellular and molecular responses to micro/nano topographies of titanium implants [40,75–77,93–111]. The molecular processes instigated by topography of implant adherent cells is of current interest. These efforts were extensively reviewed by Thalji et al. [26]. Fig. 3 illustrates the osteoinductive/osteogenic signaling pathways potentially activated within osteoprogenitor cells adherent to titanium surfaces of diverse roughness. The descriptive studies clearly define the effect of topography on adherent cell function and more recent RNAseq [112] and single-cell seq [113] studies have expanded this understanding of osteogenesis and can be more fully applied to understanding of topography effects on tissue responses leading to osseointegration or its failure. Support for this approach has been suggested by recent

studies of osteoimmunology in periodontitis where data has informed spatiotemporal gene expression, cell population and cell-to-cell interactions [114].

Human experiments performed at the level of gene expression have arrived at similar and complementary conclusion that micro- and nanotopography enhance osteoinductive/osteogenic gene expression in implant adherent cells [16,17,115]. This underscores earlier observations from human histological studies demonstrating that surface topographic modification (eg. moderately rough surface) effectively and reproducibly increase the bone to implant contact or osseointegration [116–121]. Clinical data also strongly implicate enhanced topography in the increased bone-to-implant contact and the correlated diminished risk of implant failure [122–124]. This body of work encouraged the present-day use of moderately rough endosseous implants in clinical implant dentistry.

3. Alveolar bone and the peri-implant cellular environment

The dental peri-implant microenvironment is unique because it presents an endosseous implant through mucosa to the oral environment. Dental implants are placed in the bone marrow of alveolar bone. The immediate interfacial tissues are often more bone marrow than mineralized bone and bone lining cells. The existence of alveolar bone-specific pathologies and the distinctive pattern of systemic diseases in maxilla-mandibular bones compared to other bones imply that they have a different cellular, physiological and pathological response, and bone homeostatic mechanism. Rapid remodeling, higher metabolism, occlusal stress stimulation, exposure to poly-microbial oral biofilm and microbiome, and tooth-derived inflammatory responses exist only in alveolar bones.

Recent flow cytometry and high-throughput single-cell RNA sequencing studies have provided a comprehensive landscape of alveolar bone immunomodulatory environment [126–128]. Transcriptional profiling of mandibular bone marrow-derived cells revealed 19 different cell subpopulations [127], affirming that alveolar bone presents a unique environment for bone regeneration, remodeling and repair [129]. Both precursor and immune cells account for the majority of cell components in the alveolar bone [128]. Stem/progenitor cells from maxillary and mandibular bones proliferate at more rapid rates than those from axial skeletal bones [130]. In addition, alveolar bone cells are less differentiated within the osteogenic lineage, and have lower osteoclastogenic potential [127,131]. Bone and periosteum from tissues derived from maxilla and mandible retain many properties of the neural crest (their origin) allowing to produce a faster, more extensive, and more physiologically relevant bone repair than similar bone tissues derived from the mesoderm (i.e. long bones) [132]. Neural crest-derived stromal cells in alveolar bones may preserve different stromal microenvironment for putative HSCs [126]. This local control of HSC mobilization raises the possibility that an alloplastic surface may influence HSC function.

These observations suggest a unique environment involving immune cells that function in defining the tissue/implant interface. Emerging data shed light on the “site diversity” of bone tissue and the distinct osteogenic and immunogenic properties of the alveolar bone that may influence the process of dental implant osseointegration. Animal models that employ alveolar/oral models of osseointegration (such as [133–135]) may shed additional light on

the mechanisms that underscore both the high initial success rates observed clinically as well as the challenges presented by exposing the osseointegrated implant to the oral environment. Mouse models may enable mechanistic studies that extend our understanding the cell and molecular mechanisms influencing dental implant success and failure.

4. Immunomodulation as an Ally in osseointegration

Arron and Choi coined the term “osteoimmunology” to describe the complex regulatory interactions between bone-remodeling cells and immune cells [4]. There is a bidirectional and dynamic reciprocal communication between the bone and immune cells that extends beyond the well-defined cross-talk in osteoblast-osteoclast signaling involving receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG) [136]. Immune cells express factors that modulate bone cell development and function, and bone cells provide vital signals to the hematopoietic and immune cells (reviewed in Refs. [136–145]) (Fig. 4).

The study of osteoimmunology and immunomodulation can inform our understanding of bone formation, maintenance and resorption at endosseous implant surfaces, particularly with respect to implant surface character and the resulting osteoimmune environment surrounding the implant. Implant surface character may guide immune and bone cell functions and their interaction to influence osteogenesis and bone repair, osteoclastogenesis, and immune responses that favor improved bone accrual at the endosseous implant surface. A deeper knowledge and more complete mechanistic understanding of the crosstalk between the bone and immune systems is required.

4.1. Immunomodulation is active during osseointegration

Following implant placement, the implant surface opposes the bone marrow (myeloid) tissues. Significantly, a ‘myelointegration’ is observed and indicated by a process of repair and repopulation of the disrupted bone marrow structure and its rich network of blood sinusoids with a morphologically normal mixture of parenchymal cells. The long-term presence of titanium implant in bone marrow does not disturb the microenvironmental organization of cells. The regenerated bone marrow cells coexist with the intramedullary titanium surface for an extended period of time [146]. More detailed studies of the medullary compartment response to endosseous implant placement may provide important insights into the medullary cells’ influence of bone formation at the implant surface.

Much of the osseointegration process revolves around MSCs and bone-forming osteoblasts that contribute to new bone formation. Cytokines and local immune cell factors are regulators of osteoblast formation and function [5–9]. In addition to the role of MSCs and bone forming osteoblasts, the development of classical modulators of inflammatory processes and dynamic inflammatory-related gene reprogramming has been reported to be a prerequisite for the differentiation of osteoprogenitor cells [147]. This is a complex process as illustrated by the multitude of immune-derived factors that promote or hinder osteoclast differentiation and activity (Fig. 5).

Inflammation after implant placement is indispensable and irreplaceable in the process of bone formation and osseointegration. It must be controlled by moving from pro-

inflammatory to regenerative immune cell functions that empower osseointegration and not fibrous integration [148]. Growing evidence demonstrates that immune cells, their interaction with bone forming cells and the surface topographic effect influence osseointegration both *in vitro* and *in vivo* [149–154]. This is, of course, complicated by the oral environment and bacterial activation of the innate immune system. The dynamics of immune response and adherent cell populations on the titanium implant surface change over time and are influenced by implant surface characteristics, which will be discussed in the following sections.

4.2. Evidence of immune cell influence during osseointegration

The healing cascade after implant placement in bone begins with hematoma formation. The interaction between surface characteristics and serum molecules and proteins initiate many responses at the implant surface [155,156], possibly affecting later cellular functions that are relatively underexplored biophysically. The affinity for and conformation of adsorbed proteins, determined by surface characteristics, provide recognition sites for platelets and other cells to interact with the implant surface. Newer technologies such as RNAseq [112] and Single-Cell seq [113], cell flow cytometry [157], and advances in proteomics/spatial proteomics (e.g. Refs. [158,159]) offer the promise of an enhanced and detailed description of the healing cascade following implant placement. Table 1 exemplifies how titanium surface micro/nano topography can affect different immune system components.

4.2.1. The role of the complement system in immunomodulation of osseointegration—

Complement is a major serum component that is generally proinflammatory and drives the first stages of wound healing. Transgenic mice lacking complement C3 display reduced inflammation and accelerated wound healing [160]. The complement system is activated following bone wounding and targets osteoblastic cells [161]. Products of the complement system are chemo-attractants for neutrophils, macrophages, and monocytes [162].

4.2.1.1. Effect of titanium surface characteristics on the complement system.:

Titanium surface modifications influence complement activation and complement-activating titanium surfaces induced greater inflammation and lower bone formation *in vivo* [163]. The degree of osseointegration has been positively correlated to significantly higher C5aR1 levels and decreased C3 levels around the titanium implant [164]. The surface characteristics of titanium implants influence protein adhesion directly. In an *in vitro* proteomic study, 218 proteins were identified on smooth and blasted acid-etched titanium surfaces after incubation with human serum, 30 of which were associated with bone metabolism. Apo E, antithrombin and protein C adsorbed mostly onto blasted and acid-etched Titanium, whereas C3 and immunoglobulins were found predominantly on smooth Titanium surfaces. Increased surface hydrophilicity significantly decreased complement adsorption [165]. Annealed and non-annealed titanium surfaces possess different protein adsorption characteristics and differ in their interactions with humoral cascade systems, complement and intrinsic pathway of coagulation *in vitro*. A lowered IgG mediated complement activity on annealed titanium surface was shown [166]. Enhanced surface topography and hydrophilicity influence complement activation that may alter bone-to-

implant contact. The possible direct (acting on osteoprogenitors (e.g. Refs. [167,168])) or indirect (acting on immune cells or endothelial cells (e.g. Ref. [169])) mechanism(s) of action remain to be fully elucidated. Questions such as early effects of surface topography on complement's role in confronting oral bacterial contamination remain to be answered.

4.2.2. The role of platelets in immunomodulation of osseointegration—Among the first cells adhering to endosseous implants are platelets. Platelets adhere within the implant-adherent fibrin matrix that serves as a scaffold for migration (osteoconduction), proliferation, and differentiation of leukocytes and mesenchymal cells at the peri-implant site [170–172]. Platelets play a role in the regulation of progenitor and leukocyte function in response to titanium implants *in vivo* [173] by releasing factors including TGF-β, IGF-1, VEGF and PDGF that are critical to establishing an osseous interface at the implant surface [172,174, 175]. VEGF and PDGF contribute to angiogenesis that occurs within the peri-implant gap during the first 7 days following implantation [174]. Platelets support a vascular-rich granulation tissue that contributes to MSC recruitment and residence, providing foci for osteogenesis [170–172]. Implant surface nanotopography enhances the development of adjacent blood vessels *in vivo,* supporting the associated contact osteogenesis [176,177]. Both surface topography and surface chemistry appear to influence integrin mediated platelet attachment and activation *in vitro* [174]. The influence of implant surface topography on platelet activation and cytokine release demonstrates one of several mechanisms acting early in osseointegration. How this affects or is affected by altered inflammatory environments merits experimental consideration.

4.2.2.1. Effect of titanium surface characteristics on platelets.: Smooth machined titanium surfaces show higher adhesion of platelets but reduced activation while the rougher surfaces demonstrate reduced platelet adhesion but near 100% platelet degranulation with the release of factors that promote bone formation at the implant surface. Increased implant surface topography and hydrophilicity both promote platelet activation and cytokine release *in vitro* and *in vivo* [172,174]. Hyperhydrophilic micro-rough titanium surfaces increase platelet activation and blood clot formation compared to untreated micro-rough titanium surfaces *in vitro* [178].

Reducing adhesion and denaturation of fibrin/fibrinogen, increasing platelet activation/degranulation, and decreasing thrombus formation may favor enhanced osseointegration. Surface modification strategies to improve titanium hemocompatibility and improve blood–implant surface interactions have been extensively reviewed by Manivasagam et al. [179].

4.2.3. The role of neutrophils in immunomodulation of osseointegration—Neutrophils are abundant in alveolar bone marrow [127,128]. Neutrophils are rapidly mobilized to the implant surface following implantation in the early inflammatory stage, and are key in recruiting macrophages and other immune cells to the injury site [180]. In addition to their phagocytic activity, neutrophils also contribute to modulating immune responses by other cells. Neutrophils play a role in immune regulation to recruit macrophages through IL-1β, CXCL1–3, TNF-α, and myeloperoxidase -generated ROS [181]. Neutrophils exhibit pro- and anti-inflammatory phenotypes, although these

phenotypes are not as well-characterized as those of macrophages [182]. The crosstalk between neutrophils and implant adherent cells is illustrated in Fig. 6.

4.2.3.1. Effect of titanium surface characteristics on neutrophils.: Neutrophils have only recently been considered as mediators of osseointegration. They are sensitive to different titanium surface properties and exhibit differential activation in response to alternative surface cues (Fig. 6). Aside from their importance in clearing the implant surface of foreign materials, neutrophils can direct next phases in immunomodulation by influencing macrophage polarization. This process is implant-surface specific; implant surface characteristics can modulate the attachment and activation of neutrophils and subsequent macrophage polarization by neutrophils *in vitro* [151,152,183,184]

Conditioned medium from smooth titanium-adherent neutrophils enhanced pro-inflammatory macrophage polarization compared to that from rough titanium-adherent neutrophils [151]. The initial inflammatory response to rough hydrophobic titanium implants was shown to be characterized by neutrophil extracellular traps (NETs) formation (NETosis) *in vitro* [185]. NETs are extracellular web-like structures composed of neutrophil proteins and DNA; they trap and kill microorganisms. When uncontrolled, NETs are affiliated with inflammatory disease [186]. NET release on surfaces regulates thrombosis, fibrosis, and tissue integration. NETs may enhance thrombin generation and coagulation on implants [187]. Hydrophilicity on titanium appears to decrease NETosis occurring more readily on hydrophobic surfaces. Neutrophils secrete higher levels of pro-inflammatory cytokines and enzymes on smooth or rough hydrophobic surfaces compared to those on rough-hydrophilic surfaces. This behavior was associated with decreased macrophage inflammatory activation in co-culture and was affirmed when NET formation was inhibited pharmacologically [151]. These studies demonstrate the intricate interactions of immune cells active at the implant surface to modulate subsequent bone formation events. Whether or not neutrophils are therapeutic targets for either local or systemic control of osseointegration remains to be determined.

Long-term animal study of the interactions of circulating neutrophils with titanium implants revealed no systemic inflammatory response, and no deleterious neutrophil activity neither in the inflammatory phase of the repair process nor after 4- and 10-months evaluation after implant insertion [173]. The early topography-dependent function of neutrophils contributes to immunomodulatory control of interfacial osteogenesis.

4.2.4. The role of dendritic cells in immunomodulation of osseointegration—

Dendritic cells (DCs) are uncommon among the leukocytes in the peri-implant compartment. DCs are antigen presenting cells and a type of phagocyte that have similar roles in healing as macrophages, promoting early inflammation and resolving late inflammation [188]. Notably, DC-deficient animals have no skeletal defects [189]. However, immature DCs may benefit osseointegration by secreting high levels of anti-inflammatory cytokine IL-10 and TGF-β [153,190,191]. Interestingly, DCs can develop into tolerogenic DCs that protect against titanium particle-induced inflammatory processes by releasing anti-inflammatory cytokines such as IL-10 [192]. Titanium particle effects are clearly mediated by immune cells, and impact both the immediate and longer-term effects on osseointegration (reviewed in Ref.

[193]). These relatively rare cells may play a role in long-term immunomodulatory control of bone-implant interface [194].

4.2.4.1. Effect of titanium surface characteristics on dendritic cells.: Changes in surface roughness and hydrophilicity induce surface specific response in DCs. A hydrophilic rough titanium surface induced an immature or anti-inflammatory phenotype in DCs *in vitro* [190,191], potentially supporting osteoblast differentiation by suppressing local inflammation [190]. In contrast, both smooth and rough hydrophobic titanium surfaces induce pro-inflammatory DC phenotypes *in vitro* [153, 190] which reduce osteoblastic differentiation via the P38 MAPK pathway [153]. Further exploration of how surface topography influences DCs control of interfacial bone formation is required.

4.2.5. The role of macrophages in osseointegration—Macrophage interactions with osteoprogenitor cells during bone formation is well defined [145]. These interactions also have been observed among implant adherent cells *in vivo* [154]. It is now well accepted that macrophages play a role in modulating the cellular responses at endosseous titanium implant surfaces. Macrophages are relatively abundant in alveolar bone, are involved in all stages of bone repair and homeostasis, and extensively interact with progenitor and stem cells [128,195]. OsteoMacs are resident macrophages located along the bone surface in close contact to mature osteoblasts at the site of bone modeling and are necessary for the mineralization of bone matrix by osteoblasts [196]. OsteoMacs are present in all phases of the intramembranous ossification [197] indicating their specific role in osteoblast function. Early osseointegration is impaired when macrophages are depleted from mice [149], showing that macrophages play a role in bone regeneration around endosseous implants.

Macrophages can rapidly change their function in response to environmental signals. Macrophage plasticity and polarization direct the inflammatory response and determine their functionality during the different stages of inflammation. This plasticity is now known to be central to the osseointegration process. At the implant/tissue interfaces, the macrophage demonstrates dynamic functions and pivots from protective, pro-inflammatory function to anti-inflammatory and wound healing roles that promote osseointegration [150] (Fig. 7). However, the comprehensive role of the dynamics of macrophage plasticity may not be fully mirrored by the M1/M2 subpopulations paradigm, and factors that drive them towards either a regenerative or pro-fibrotic phenotype are incompletely known [198,199]. Macrophages adherent to the dental implant surface, their plasticity and phenotype, and the impact of these cells on osseointegration is the focus of current intensive investigation *in vitro* and *in vivo*.

4.2.5.1. The role of M1 macrophages in osseointegration.: Macrophages adopt a classically activated (M1 or pro-inflammatory) state in their early interactions with implanted titanium surfaces. Interestingly, macrophages derived from circulating monocytes possess proinflammatory role in comparison to macrophages that are tissue resident [200,201], implying a role for monocytic-derived cells in initiating the inflammation around implants. They release pro-inflammatory cytokines that aid in directing the phagocytotic clearing of the surface and removal of dying neutrophils, dead bone tissue and necrotic

debris by releasing proteolytic enzymes and reactive oxygen species. TNF-α, IFN-γ, IL-1β and IL-6 secreted by M1 macrophages stimulate the infiltrating and local T cells [202]. If unchecked, this pro-inflammatory response to implanted materials would impair the osseointegration process.

M1 macrophages also produce osteoinductive factors. Most prominently, Oncostatin M (OSM) secreted by M1 macrophages is an osteogenic cytokine and may have a regulatory role predominantly in the early phase of peri-implant bone regeneration by contributing to MSC recruitment, proliferation and differentiation, angiogenesis and matrix deposition [203–208]. OSM receptors are highly expressed in alveolar bone MSCs and osteoblasts [128]. In addition, OSM stimulates osteoblasts to secrete RANKL *in vitro* [209], promoting osteoclastogenesis and bone remodeling (Fig. 7). M1 macrophages also recruit MSCs by secreting the highest levels of chemo attractants, CCL2 and VEGF [150]. These underscore the potential significance of M1 macrophages in the control of interfacial osteogenesis through OSM. OSM is a prominent osteogenic factor produced by these cells and is now widely implicated in activating MSC osteogenesis. How this is temporally linked to subsequent M2 macrophage activities or whether it is the predominant osteogenic factor produced over the period of macrophage function in osteogenesis requires further investigation.

4.2.5.2. The role of M2 macrophages in osseointegration.: Temporal regulation and orchestrated transition of a surface-adherent population rich in M1 macrophages to one rich in M2 macrophages is required to move healing from the requisite inflammatory to regenerative phases of bone healing in the regulation of osseointegration. M2 macrophages improve interfacial osteogenesis by their production of cytokines, chemokines and growth factors, such as BMP-2, TGFβ, PDGF, and IL-10, leading to recruitment and differentiation of osteoblasts on the implant surface [150,210–213] (Fig. 7). An early demonstration of BMP-2 expression by cultured and titanium adherent macrophages suggested that macrophages may contribute surface-specific osteoinductive signals during bone formation at implanted alloplastic surfaces [214,215]. Later, further evidence of secretion of osteogenic factors by titanium adherent macrophages and their specific subtypes was demonstrated both *in vitro* and *in vivo* [150,210,213–221].

In addition, these alternatively-activated macrophages modify extracellular matrix (ECM) turnover by regulating the balance of matrix metalloproteinases (MMPs) and their tissue inhibitors [222], inhibiting osteoclastogenesis [211,223] and promoting angiogenesis [224]. A close crosstalk between macrophages and reestablishing vessel network during bone repair also has been shown [225]. Stimulation of angiogenesis is a synergistic effect of M1 and M2 macrophages with secretion of VEGF and OSM by M1 and PDGF by M2 macrophages [128,150,226, 227] (Fig. 7). Furthermore, an angiogenic M2-like macrophage subtype develops from M1 macrophages under the *in vitro* stimulation with Toll-like receptor (TLR) agonists and adenosine [228]. A prolonged pro-inflammatory microenvironment leads to a persistence of anti-regenerative cells and an inhibition of osteoblastogenesis with simultaneous stimulation of osteoclastogenesis.

The increased M2 macrophage number and higher M2/M1 macrophage phenotype balance was correlated to the proximity and volume of bone growth at the titanium implant vicinity after 10 days *in vivo* [229]. A higher M2/M1 population ratio may reflect the early recruitment, survival and osteogenic functions of the cell populations at the implant interface that contribute to successful osseointegration. How topography controls the M2/M1 population may be an important factor controlling the process of interfacial bone formation at implant surfaces.

4.2.5.3. Effect of titanium surface characteristics on macrophages.: There exists a correlation between the early macrophage response to titanium surface topography and the outcome of bone remodeling. The initial M1 response is independent of surface topography and spatial confinement [230]. Therefore, the transition to pro-healing/anti-inflammatory state appears to be implant surface topography-dependent. As these cells produce proinflammatory cytokines as well as the osteogenic factor OSM, how the duration of M1 residence upon an implant surface is influenced by surface topography may be an essential aspect of immunomodulation in osseointegration.

It is known that physical and mechanical factors co-regulate macrophage attachment, plasticity and phagocytosis [231–236], and tailoring biomaterials to modulate macrophage fate and phenotype is of significant interest [141,180,237–240]. Titanium implant surface characteristics including topography and wettability are known to influence macrophage attachment, activity and phenotype [104,154,157, 213,215,217,219,241–249]. An implant surface presents a relatively (infinitely) rigid surface. In general, the polarization state of macrophages is closely related to the physical nature of their adherent substrate. Topographically enhanced surface-mediated elongation is associated with an M2-like phenotype and enhances the effects of M2-inducing cytokines as well [235]. This sheds light on how titanium surface topography-dependent changes in macrophage phenotype promotes osseointegration, yet needs further mechanistic investigation. Previous *in vitro* and *in vivo* studies also highlighted cytoskeleton-related mechano-transduction playing a pivotal role in the topography-induced osteoinductivity, polarization and immunomodulatory properties of macrophages on titanium [177,213,215,217,219]. However, how the cytoskeleton tension regulates macrophage polarization still remains largely unknown.

4.2.5.3.1. The role of titanium surface nanotopography in macrophage polarization.: More recent investigations have highlighted the impact of surface topography on adherent macrophage function in osseointegration. Micro-roughness mediates both pro- and anti-inflammatory macrophage polarization [241,242,244,245,247,250–252]. Anti-inflammatory macrophage polarization (M2-like) was enhanced over a small range of micro-roughness (Ra = 0.51–1.36 μm; Sa = 0.66–2.91 μm), while roughness outside of the range upregulated a mixture of pro- and anti-inflammatory markers [245]. Micro-rough titanium surface was shown to increase BMP-2 expression and secretion in macrophages [215,216].

Nanotextured titanium surfaces can promote anti-inflammatory rather than pro-inflammatory macrophage phenotypes [175,177,213, 217,221,247,248,253–257]. Titanium surfaces with 100 nm diameter nanotubes favored an M1 macrophage phenotype, while those with 30 nm diameter favored M2 polarization, increased MSCs osteoblastic differentiation in co-culture

and induced better osseointegration *in vivo*. Osseointegration of 100 nm nanotube surfaces significantly improved in mice in which M1 macrophages were restrained [254]. FAK-MAPKs signaling (JNK and Erk1/2) were involved in macrophages M1 polarization induced by this surface [258], while attenuation of macrophage inflammatory activity occurred with the surface-specific inhibition of MAPK and NF-κB pathways [255]. While nanotubes of varying diameter represent one type of nanoscale surface that can be nonlinearly applied to clinical dental implants, other discrete nanofeatures have not been broadly explored.

A titanium hierarchical nano surface (nanoscale features superimposed on micro scale roughness) significantly upregulated the gene expression of M2 markers and BMP-2 in macrophages as well as specific receptors of BMP-2 such as BMPR2 and BMPR1A in MSCs leading to their enhanced osteogenic differentiation *in vitro* [217]. Micro/sub-micro hierarchical titanium surfaces promoted an M2 phenotype and inhibited M1 macrophage-mediated inflammatory reactions via suppression of the TLR2/NF-κB signaling pathway and promoted osteogenic differentiation of MSCs by modulating macrophage polarization *in vitro*, all of which translated to enhancing early osseointegration in rats [256]. A micro-rough titanium surface with superimposed nano-flakes and nano-wires structures (micro/nano) polarized macrophages to M2 phenotype and increased BMP-2, BMP-6 and TGF-β expression in M2 macrophages compared to the rough surface. This improved osteoblastic differentiation on the micro/nano surface [221]. Titanium surfaces with nanoscale (90 nm) honeycomb-like TiO2 structures reinforced the M2 polarization of macrophages through the activation of the RhoA/Rho–associated protein kinase signaling pathway and induced subsequent BMP-2 expression, again suggesting the role of cytoskeletal signaling and cell shape effects on macrophage polarization. The surface adherent population favorably triggered osteogenic differentiation of MSCs *in vitro* and improved osseointegration *in vivo* [213]. A rough titanium surface induced increased OSM expression in adherent monocytes and enhanced MSC differentiation in co-culture [259]. Another study did not find significant differences in OSM mRNA and cytokine levels from macrophages cultured on smooth and honeycomb-like TiO2 nano-structures [213]. Here, a brief focus was created on macrophage-osteoblast functions and M1/M2 ratios with evidence that both M1 (via OSM) and M2 macrophages (via BMP-2, TGF-β etc.) promote osteoinduction and osteoblast function in bone repair.

A micro/nano titanium topography promoted osteogenic differentiation *in vitro* by induction of exosomes that mediate macrophage-MSC osteogenic crosstalk [260], adding to the complexity of paracrine regulation of osteogenesis that is influenced by the implant surface topography. The impact of implant surface topography on monocyte paracrine control of osteoinduction requires further investigation of soluble, cell-to-cell, and cell-ECM/surface interactions.

4.2.5.3.2. The role of titanium surface hydrophilicity in macrophage polarization.: Surface wettability or hydrophilicity is a second significant modulator of cell responses and bone formation at implant surfaces, and it modulates the anti-inflammatory activation of macrophages. The combination of roughness and hydrophilicity to suppress proinflammatory markers has been repeatedly shown to enhance the anti-inflammatory macrophage phenotype [154,241,242,251,252, 261–263]. A hydrophilic nanostructured

titanium surface successfully compensated for the compromised M2 macrophage function of Type 2 diabetic rats by attenuating the pro-inflammatory response and promoting M2 macrophage activity, that favored osseous healing [263].

In a mouse study, an initial increase in local and systemic proinflammatory markers and elevated monocyte/macrophage markers was observed one day following placement of rough hydrophilic implants compared to hydrophobic implants with the same surface topography [154]. Differing levels of cytokines were measured in circulating plasma based on implant surface properties. An increased level of pro-inflammatory IL12p40 was detected in circulation of mice receiving rough hydrophilic titanium implants compared to rough titanium after 24 h. Mice with rough hydrophilic implant also displayed higher IL10 levels. The levels of IL12p40 were reduced after 3 days in the hydrophilic versus the hydrophobic group. After 7 days, there was a further increase in IL10 and still lower levels of IL12p40 in mice with hydrophilic implants [154], indicating immunomodulation favoring reduced inflammation and enhanced bone formation.

The mechanism(s) controlling cellular responses to hydrophilic titanium surface modulation of the M2 macrophage phenotype *in vitro* includes interactions of β1 integrin with adsorbed fibronectin followed by activation of the PI3K/Akt signaling pathway. Additionally, macrophages adsorbed onto the hydrophobic titanium surface interacted with adsorbed fibrinogen through integrin β2 resulting in the generation of M1 macrophages most likely involving NF-κB activation. Further, hydrophilic surface induced BMP-2 and TGF-β expression in macrophages and positively affected osteoblastic differentiation [219]. In a mouse study, microstructured hydrophilic titanium surfaces modulated Wnt signaling gene expression in macrophages through integrin signaling, and Wnt signaling mediated anti-inflammatory macrophage polarization [104] that can promote osteogenic differentiation of MSCs [264,265] in response to topographical cues particularly though BMP signaling [264]. This Wnt dependent mechanism has been observed *in vivo* [104]. The loss of Wnt signaling attenuates macrophage polarization, and this was associated with decreased recruitment of MSCs and CD4 T-cells [104]. The local delivery of a Wnt protein therapeutic in a rat model improved osseointegration in an unstable implant placed into an oversized osteotomy and in cases where fibrous encapsulation was predominant [266,267].

The above examples demonstrate that the surface-mediated modulation of macrophages works both directly and indirectly with osteoblastic cells to influence osteoinduction and bone formation. Other examples include the macrophage response to a rough-hydrophilic titanium surface influencing T-helper cell populations and MSC recruitment [154]. These findings highlight that immunomodulatory topographies may direct implant-adherent macrophage via two possible scenarios. The first strategy minimizes the initial M1 reaction (temporally and/or quantitatively), while the second focuses on advancing temporally and/or quantitatively the dominance of M2 macrophages. Both strategies recognize the necessity of M1 macrophages during wound healing and osteogenesis and identify the role of M2 macrophages in osteoinduction and osteogenesis. Macrophages adherent to implant surfaces with enhanced surface topography positively contribute to the osseointegration process.

It should be emphasized that the impact of implant surface physical properties as exemplified by hydrophobicity, while often interrogated at the cellular level, is mediated largely surface-adsorbed protein effects. A recent review indicates that multiple surface features impact protein abundance and conformation to influence adherent cell behavior [268].

4.2.6. The role of T cells in immunomodulation of osseointegration—There is emerging evidence supporting the role of T cells in bone repair and regeneration through modulation of inflammation during the healing process [269] (Fig. 8). Naive T cells differentiate into either $CD4^+$ T helper (Th) cells or $CD8^+$ cytotoxic (effector) T cells which can exert negative or positive effects on bone healing [270]. $CD4^+$ T cells are further divided into Th1, Th2, Th17, and regulatory T cells (Treg) and differ in the cytokines produced and their function [271]. A consistent upregulation of $CD4^+$ and downregulation of $CD8^+$ cells was observed around titanium implants placed in rabbit tibia after 10 days, indicating a CD4-lymphocyte phenotype driven reaction [229].

Individual T cell subsets, upon their activation, affect osteoblast maturation through the production of soluble factors. The proinflammatory T cells, including the T helper 17 cells, are most stimulatory for osteogenesis *in vitro* [272]. Effector/regulator T cell ratios impact bone regeneration and bone healing outcomes [270]. Terminally differentiated $CD8^+$ T cells secrete TNF-α and IFN-γ [273] which have inhibitory effect on osteogenic differentiation capacity of MSCs [270] and negatively affect bone regeneration in humans [274]. T helper cell function depends on physiological or pathological conditions [6,275] and T helper cell subsets (Th1, Th2, Treg and Th17) can be transformed into each other [276]. Reducing the number of Th1 and Th17 cells in the local microenvironment might improve the survival and osteogenic differentiation of the MSCs [276]. Th2 cells can activate macrophages toward an anti-inflammatory phenotype to reduce inflammation [277]. Treg cells are abundant in alveolar bone [127] and mainly have an anti-osteoclastogenesis function by secreting TGF-β, IL-4, and IL-10 [278]. Accounting for the temporal distribution of T cell phenotypes at and surrounding endosseous implants is incomplete and may contribute to further understanding of immunomodulatory control of osseointegration. The implied role of T cells in the osseointegration process suggests that systemic diseases or conditions that influence various T cell function or abundance may be contributors to otherwise unexplained failure of osseointegration. This idea is supported by mouse model studies in which CD4 and CD8 T cell levels were manipulated to alter bone repair in a non-critical size mouse femur osteotomy model [270].

Although M1/M2 macrophage activities exist without T cell influence, specialized or polarized T cells (Th1, Th2, Treg) play a role in macrophage polarization [279,280], and the transition of cytokine profiles from Th1 to Th2 cells is related to the M1/M2 phenotype [276]. M1 macrophages promote Th1 cells to secrete inflammatory cytokines such as IL-2, IFN-γ, TNF-α, TNF-β; and M2 macrophages contribute to the secretion of cytokines such as IL-4, IL-5, IL-6, IL-10, IL-13 by Th2 cell *in vivo* [276,281,282], highlighting the importance of the interaction between macrophage and T cells for bone formation and maintenance. Further work is needed to understand the role of adaptive immunity in the process of osseointegration.

4.2.6.1. Effect of titanium surface characteristics on T cells.: The influence of surface topography on T cell function in osseointegration is rarely studied, although a recent *in vitro* report indicated that nanotubes (105 nm) increased T cell FGF-2 production by blocking key MAPK pathways to increase MSCs proliferation [283]. Increased surface roughness and hydrophilicity was shown to polarize the adaptive immune response towards a Th2, pro-wound healing phenotype, leading to faster resolution of inflammation and increased stem cell recruitment around rough hydrophilic titanium implants placed in mice [154]. T-helper cell profiles changed as early as 3 days post-implantation. Rough hydrophobic titanium implants increased Th1 as well as Th2 and Treg phenotype factors compared to control in adjacent bone marrow. Rough-hydrophilic titanium generated the greatest up-regulation of Th2 and Treg genes, while simultaneously reducing Th1 genes at day 3 [154] (Fig. 8).

In an animal study, endosseous implant-associated changes in T-cell populations were shown to extend to contralateral leg bone marrow and spleen. Titanium implants with rough and rough-hydrophilic surfaces changed the T-helper cell profile by decreasing Th1, Th17, and Treg populations and increasing Th2 cells in bone marrow of the contralateral leg with no implant. A decrease in Th1 and Th17 cells and increase in Treg population was also observed in the spleen of experimental animals [154]. These results suggest that either antigen presenting cells travel from the implantation site and re-enter the lymph node and exert these effects or the soluble factors produced from implant adherent or adjacent cells affect other T-cells systemically. Further studies are needed to better understand the possible systemic immune influence of titanium implant placement.

This brief overview of possible T cell activities in osseointegration illustrates the complex and early stage immunomodulatory environment that is established on and proximal to the titanium implant surface (Fig. 8).

4.2.7. The role of B cells in immunomodulation of osseointegration—B cells participate in the process of bone repair and predominate the later stages of bone healing [284]. B cells may play a temporal regulatory role in osseointegration by secreting OPG and RANKL to control bone formation/resorption [285]. B lineage cells are not perturbed by the long-term presence of titanium implant in bone marrow and B cell differentiation in bone marrow around endosseous implants is considered an index of myelointegration [146]. Studies regarding the role of B cells in osseointegration are rare. Additional studies are required regarding the contribution of B cells and their secreted factors to osseointegration. The crosstalk between B cells and implant adherent cells is depicted in Fig. 9. The relative absence of studies concerning the role of B cells in the immunomodulatory control of osseointegration contrasts with the remarkable observation that the genetic knockdown of B cells in mice resulted in more trabecular bone and greater levels of bone sialoprotein mRNA than in wild-type mice [286].

5. Immunomodulation as an Enemy of Osseointegration

Dental implants are placed in the microbial-rich environment of the mouth. The complexity of osteoimmunology, the oral microbiome, and the osseous and mucosal structures surrounding implants is on full display. Fifty two different wound healing biomarkers

were identified during a 16 week evaluation of osseointegration, highlighting the complex inflammatory peri-implant environment [287]. Considering the molecular and cellular basis of osseointegration discussed above, the process of peri-implant bone loss and implant failure (absence of bone to implant contact) may be further informed by immunomodulation at an implant surface. Peri-implant bone loss is an etiologically diverse phenomenon with shared immune-mediated chronic inflammatory processes leading to ineffective or insufficient bone apposition by osteoblasts, the excessive differentiation and activation of osteoclasts, and prolonged osteoclastogenic signals by immune and local stromal cells [288–293].

5.1. Immunomodulation is active during peri-implant osteoclastogenesis

The induction of osteoclast function is necessary during the formative phase of osseointegration, and transiently increased numbers of osteoclasts may not be contrary to the overall accrual of bone mass by an integrated regulation of bone formation and resorption [97,294]. Clearly osteoclasts migrate to the implant site and start osteoclastic resorption and remodeling of bone debris [295,296]. Factors released during osteoclastic bone resorption regulate immune cell, and immune or inflammatory factors induce osteoclastogenesis [297].

Before expounding on the catabolic effects of osteoclastogenesis on bone accrual in osseointegration, the process of bone resorption in removal of surgically damaged bone following implant placement and the role of bone resorption to maintain bone turnover throughout the functional lifetime of a successful implant must be acknowledged. Osteoclastic activity is acknowledged to occur at early times in bone adjacent to placed implants and bone turnover has been repeatedly observed long after implant placement. The question of how implant surfaces influence osteoclast function was posed before the discovery of molecular mechanisms controlling osteoclastogenesis [298].

It is now accepted that three major cytokines (macrophage-colony stimulating factor (M-CSF), RANKL and OPG), and the RANK/RANKL/OPG signaling axis are involved in the well-defined regulation of osteoclastogenesis by immune cells [299–304]. Significantly elevated levels of prostaglandin E2 (PGE2), TNF-α, IL-1, IL-6, IL-17 and M-CSF in peri-implant inflamed tissues induce the secretion of RANKL by bone cells, activated leucocytes, dendritic cells and neutrophils [305–309]. Both soluble and membrane-bound RANKL can induce osteoclastogenesis through RANK and downstream signaling in osteoclast precursors [310–316], suggesting a role for adherent cells in this process. IL-1 and TNF-α may induce osteoclastogenesis alone in the absence of RANKL [307,317]. OPG is a decoy receptor for RANKL and prevents RANK-RANKL interactions to fine-tune osteoclast differentiation and bone remodeling. OPG is secreted by osteoblasts and bone marrow B cells and its production can be induced by IL-4, and TGFβ. Synchronously, OPG drives apoptosis of the pre-existing osteoclasts [305,318]. High OPG expression and low RANKL/OPG ratios result in the inhibition of osteolysis, while high RANKL/OPG ratio leads to peri-implant osteoclastogenesis, bone resorption and implant loosening [306, 319–321]. Osteoclastogenesis is a complex process as illustrated by the many of immune-derived factors that promote or hinder osteoblast differentiation and activity (Fig. 10). Given the prevalence of osteoporosis and the many different pharmacological approaches

to inhibiting osteoclast activity including bisphosphonates and RANKL antibodies (e. g., Denosumab), the role of osteoclasts and the impact of surface topography on osteoclasts in osseointegration merits further consideration.

5.2. Osteoclastogenesis and implant surface topography

The impact of endosseous implants surface topography on osteoclastogenesis can be considered with respect to microbial colonization and peri-implantitis, osteoclastic precursor-surface interactions, and the upstream/downstream effects of surface topography on immune cell and osteoblast (and precursor) cell function. Examples of all have been presented in the literature. The role of implant surface topography in modulation of osteoclastogenesis is demonstrated in Fig. 11. Table 2 summarizes how titanium surface micro/nano topography may affect osteoclastogenesis.

5.2.1. Direct effect of surface topography on osteoclastogenesis—Surface topography mediates osteoclast-implant interactions and contributes to defining the net bone accrual in the process of osseointegration [322] (Fig. 11). It remains to fully consider the significance of possible surface-mediated reduction in osteoclastogenesis on net bone accrual at the implant/bone interface and the process of long-term bone remodeling around implants.

The effects of nanotopography upon osteoclasts have been demonstrated *in vitro* [323]. Cytoskeletal reorganization plays role in osteoclastogenesis [324], implicating the possible role of implant surface topography in this process. In addition, titanium surface microtopography affects the assembly of the osteoclast resorption apparatus *in vitro* [325]. These effects are mediated through different topography-sensitive pathways. For example, micro/nano titanium surfaces reduce osteoclast activity and inhibit osteoclast differentiation through MAPK signaling pathway [326,327]. Additionally, titanium surface roughness (approximate Ra of 1.25 μm) facilitated osteoclast differentiation through the activation of the RANK-TRAF6 signaling network [328]. The osteoblast-osteoclasts interactions are influenced by surface topography require further investigation. For example, titanium with nanotopography attenuates the osteoclast-induced disruption of osteoblast differentiation *in vitro* by regulating histone methylation [91].

5.2.1. Indirect effect of surface topography on osteoclastogenesis—The effect of surface topography may be indirect (Fig. 11). MSCs and osteoblasts may acquire an immunomodulatory role affecting osteoclastogenesis that is surface topography dependent, for example, through modulating the fusion of new osteoclasts and reduced activity of existing osteoclasts [105]. Similarly, other immune cells that are adherent to implant surfaces may play roles in osteoclastogenesis that are also surface topography informed. Implant surface topography influences the expression of osteoclastogenic factors including TNF-α, M-CSF, OPG and RANKL by surface-adherent cells as shown both *in vitro* and *in vivo* [24,26,97,98,329,330].

Implant surface topography may influence osseointegration through modulating OPG/RANKL ratios. For example, microstructured titanium surfaces increase the production of OPG by osteoblasts *in vitro* which can inhibit the formation of osteoclasts and

therefore decrease the bone resorbing activity [97,329,330]. Titanium implants with 15 nm high disordered nanopillars increased osteogenesis, increased OPG and reduced RANKL expression. This led to decreased osteoclast formation *in vitro* and improved osseointegration *in vivo* [321]. Another study revealed the surface topography dependent MSC secretion of RANKL/OPG. MSCs on titanium surface with 30 nm nanotubes in diameter showed lower RANKL/OPG ratios while 100 nm surface had high RANKL/OPG ratio leading to significantly lower osteoclastogenesis *in vitro* and better osseointegration *in vivo* on the titanium surface with 30 nm nanotubes [331]. Another indirect mechanism at play may involve surface adherent macrophages. Titanium with micro/nano topography inhibits osteoclastogenesis via mediation of M2 macrophage polarization both *in vivo* and *in vitro* [332].

5.3. Factors that promote inflammation and osteoclastogenesis at the implant-bone interface

Site-specific, implant-related (eg, surface roughness, mechanical strain, titanium particulate debris, and excess cement), and patient-related factors (eg, genetics, diabetes and other systemic diseases) are all implicated in the initiation/progression of inflammation leading to osteoclastogenesis at endosseous implants [333–338].

5.3.1. The role of innate and adaptive immune system components in peri-implant osteoclastogenesis—Bone and immune cells dynamics, and immune response during peri-implant and alveolar bone loss have been extensively reviewed [290, 339–343]. It is suggested that the increased levels of the selected peri-implant crevicular fluid (PICF)-derived biomarkers of inflammation, matrix degradation/regulation, and alveolar bone turnover/resorption combined with site-specific microbial profiles may be associated with peri-implant bone loss and could have potential as predictors of peri-implant diseases [344].

Both innate and adaptive immunity may be involved in the inflammatory challenges facing endosseous implants success. Innate immunity involving neutrophils, macrophages, dendritic cells, and T cells in the tissue surrounding the endosseous implant leads to osteoclast-mediated peri-implant bone loss. Adaptive immune responses to foreign substances include T cell and B cell responses and can develop over time through exposure. Innate and adaptive immune responses induce bone loss by means of multiple immune receptors, inflammatory cytokines (e. g. IL-1β, IL-6, IL-12, IL-17, TNF-α, IFN-γ, IL-8, monocyte chemo-attractant protein-1, macrophage inflammatory protein-1α), and matrix metalloproteases through RANKL, Notch, Wnt, and NLRP3 inflammasome signaling pathways [290,345–352] (Fig. 11). The activation of inflammatory signals within MSCs or osteoprogenitors inhibits osteoinductive signaling and osteogenesis. Similar inflammatory mediators promote osteoclastogenesis. Unregulated, continued inflammation results in the failure of bone formation at the implant surface.

5.3.1.1. The role of the inflammasome in peri-implant osteoclastogenesis.: NLRP3 inflammasomes are important regulators of IL-1β activity and release from multiple cells that populate the implant surface in response to pathogen- and injury-related

signals (DAMPs and PAMPs) [345]. Inflammasome activation in bone-resident and circulating macrophages promotes M1-like macrophage polarization [353–356]. NLRP3 is a prerequisite for osteoclast maturation [357]. The role of the NLRP3 inflammasome in inflammatory alveolar bone resorption has been highlighted *in vivo* [358,359]. It drives the peri-implant bone loss via caspase-3/GSDME [360], along with several alternative inflammation pathways that function in peri-implantitis such as the LOX-1/MMP9 signaling pathway [361], TLR2/NF-κB/MAPK/JNK pathway [362, 363], and Erk1/2/MAPK pathway [364]. The NLRP3 inflammasome may also play role in inflammatory alveolar bone resorption by inducing pyroptosis [360,365–368]. The NLRP3 inflammasome alters the RANKL/OPG ratios to enhance osteoclastogenesis [369], suggesting its role in mediating the net accumulation of bone at the implant/tissue interface.

There is evidence that surface topography may influence inflammasome function. NLRP3 inflammasome can enhance osteoclast bone resorption ability *in vivo* by reorganizing the actin cytoskeleton [370], and cytoskeleton F-actin microfilaments inhibit NLRP3 inflammasome activity in macrophages. This inhibition depends on the actin polymerization state [371]. Titanium with nano-sized crystalline hydroxyapatite significantly upregulated Caspase1 expression in differentiating osteoblasts which further suggests an involvement of the inflammasome complex [372]. Although no other studies have been performed linking the inflammasome pathway to implant surface topography, titanium particles and ions appear to increase expression of inflammasome proteins and function in peri-implant cells [373–377].

5.3.1.2. The role of NF-κB signaling pathway in peri-implant osteoclastogenesis.: NF-κB signaling pathway regulates inflammatory protein expression in macrophages and MSCs [378,379]. NF-κB is in the upstream of inflammasome pathway and is the transducer of priming signals necessary for pro-IL-1β transcription and assembly of NLRP3 inflammasome compartments [367,380,381]. Inflammation driven by NF-κB activity is known to be a primary activator of peri-implant osteoclastogenesis and osteoclast function both *in vitro* and *in vivo* [382,383]. The NF-κB pathway inhibits the production of BMPs that diminishes the BMP2-stimulated Runx2 and Wnt-stimulated β-catenin binding to Osteocalcin and bone sialoprotein promoters [313,384]. The NF-κB cascade was identified by gene ontology analysis of changes in gene expression in rough implant-adjacent cells at day 4 following implantation, underscoring a transient role for inflammation in control of osseointegration [17]. A subsequent study compares a rough vs. rough/hydrophilic surface implants in the same model without identifying changes in inflammatory signaling [385]. Further examination in the context of systemic inflammatory determinants (e.g., chronic inflammatory diseases, aging) could reveal additional surface topography influences on NF-κB-related pathways affecting immunomodulation [386].

Titanium surfaces of various roughness differentially activate the early NF-κB transcriptional pathway in macrophages *in vitro*, with rough hydrophilic surfaces having minimum activation compared to smooth surface [382]. The NF-κB nuclear translocation was decreased on a micro/sub-micro-textured titanium surface [256]. This is thought to be an integrin-mediated event [387], however, other mechanisms have been implicated in cell culture [382]. In a therapeutic approach targeting NF-κB, the inhibition of NF-κB signaling

in implant adherent cells was achieved by the binding of NBD (NF-κB essential modulator (NEMO)-binding domain) peptide to titanium implant surfaces. In addition to demonstrating reduced osteoclast activity in cell culture on the NBD modified surface, *in vivo* studies using NBD modified implants demonstrated that this inhibition of NF-κB signaling also reduced the local osteoclast population and was associated with an increased bone to implant contact in an ovariectomized rat model [383]. There exist multiple approaches to inhibition of NF-κB signaling that may be synergistically applied with the topographic modification of the dental implant surface.

5.3.1.3. The role of toll-like receptors in peri-implant osteoclastogenesis.: Toll-like receptors (TLR) are sentinel receptors of the innate immune system and play a central role in innate immunity. TLR activation in osteoclasts and their precursors is an important aspect in the pathogenesis of inflammation-induced bone resorption [388–390]. TLR-induced production of TNF-α and IL-6 promotes functional osteoclast differentiation in synergy with RANKL both *in vivo* and *in vitro* [391,392]. TLR 2, 4, 5, and 9 are expressed on osteoblasts and their activation increases osteoclast differentiation *in vivo* and *in vitro* by an indirect mechanism through stimulation of RANKL [388]. TLR2/4 knockout mice showed significantly less bone resorption compared to WT mice in ligature-induced experimental peri-implantitis using smooth surfaced implants. Gingival injection of anti-RANKL antibody significantly reduced bone loss compared with the ligation only group in both WT and TLR2/4 KO mice [393]. TLR4 was shown to mediate alveolar bone resorption in experimental peri-implantitis around smooth surfaced implants through regulation of immune B cell infiltration, RANKL/OPG ratio, and inflammatory cytokine production *in vivo* [389]. In a human model of peri-implantitis, a TLR4 induced inflammatory cytokine production and extracellular matrix breakdown was demonstrated [390].

Macrophage exposure to smooth titanium surface displayed an enhanced immune response to TLR4, TLR7 or TLR2/1 compared to rough surfaces in terms of soluble immune mediators secreted and M1/M2 gene expression profiling [394]. A micro/sub-micro-textured titanium surface yielded the least TLR2 expression in cultured macrophages compared to smooth surface [256]. A reduction in TLR3 expression was reported in macrophages cultured on rough titanium surfaces compared to machined surface. TLR downstream signaling was regulated in a roughness-dependent manner [394]. Melatonin was shown to reduce peri-implantitis through inhibiting TLR4/NF-κB signaling and osteoclastogenesis around micro-rough titanium implants *in vivo* [395]. Nonetheless, the overall effect of TLR pathway regulation by surface topography on cytokine responses in peri-implant bone loss and subsequent protective versus pathogenic signals in this process need further investigations.

5.3.1.4. The role of complements in peri-implant osteoclastogenesis.: Complement-dependent mechanisms of inflammatory alveolar bone destruction have been demonstrated [396]. C3 activation induces osteoclast differentiation and C3 knock-out bone marrow cells exhibited lower RANKL/OPG expression ratios, express lower M-CSF and IL-6, and generated significantly fewer osteoclasts [310]. Increased C3 was detected in the serum and surrounding tissues near by the titanium implants with increased inflammation and

osteoclast formation. C3a/C3aR, and not C3b, played an important role in NF-κB mediated secretion of TNF-α and MMP9 leading to differentiation and proliferation of osteoclasts [397].

5.3.1.5. The role of dendritic cells in peri-implant osteoclastogenesis.: DCs are key players in osteoimmunology and have been implicated in inflammation-induced bone loss through the activation of $CD4^+$ T cells leading to induction of osteoclastogenesis [297,398,399]. Mature DCs increase the secretion of inflammatory factors such as IL-12 and facilitate the activation of T-cells and B-cells, which enhance inflammation and may impede peri-implant interfacial bone formation [153,190,191]. Dendritic cells may also transdifferentiate into osteoclasts at their early development stage, and IL-1β may increase the fusion of dendritic cells into osteoclasts [400,401]. These osteoclasts produce higher IL-1β compared to osteoclasts derived from monocytes, which further induces TNFα-producing $CD4^+$ T cells and promotes bone resorption [402].

Smooth and rough hydrophobic titanium surfaces switch DCs toward maturation phenotypes, increase the expression of IL-6, IL-12, IL-18, and TNF-α, inhibit the differentiation and mineralization of osteoblasts and promote osteoclastogenesis *in vitro* [153,190]. DCs on smooth titanium surface release MCP-1 [190] which induces osteoclastogenesis and the formation of multinucleated osteoclast-like cells from bone marrow precursors *in vitro* and can induce bone resorption with RANKL [403, 404].

5.3.1.6. The role of macrophages in peri-implant osteoclastogenesis.: Macrophage polarization plays major roles in peri-implant bone loss [405–408]. Bacterial products or interferons present in peri-implant tissue promote M1 phenotype, and M1 macrophages constitute a majority of inflammatory cellular composition in histopathological observations of human peri-implantitis lesions [406,408–410]. M1 macrophages are involved in peri-implant osteoclast activities by secretion of high levels of TNF-α and IL-1β, as well as being the potential precursor of osteoclasts under the stimulation of M-CSF and RANKL [307,339,341]. Furthermore, these macrophages can express RANK, RANKL, and M-CSF, which enable self-activated osteoclastogenesis [306]. Interestingly, macrophages isolated from inflamed peri-implant tissue were found to differentiate into mature osteoclasts without accompanying osteoblastic cells or MSCs, and expressed higher RANKL mRNA compared to OPG mRNA [411]. M1 macrophages also induce the Th17 polarization of CD4 cells that produce IFN-γ, IL-17, and IL-21 leading to more osteolytic effects *in vivo* [412]. The mechanism and regulators of the differentiation of macrophages into osteoclasts, and the role of macrophage-osteoclast axis in bone loss caused by inflammation has been extensively reviewed [413]. All of these findings demonstrate that peri-implant macrophages can differentiate to active osteoclasts in the presence of M-CSF via two pathways: direct stimulation from IL-1 and TNF-α or by binding to RANKL secreted from the various cells mentioned above, elucidating how chronic inflammation rapidly cascades into severe peri-implant osteolysis and bone resorption.

Implant surface topography affects macrophage-mediated osteoclastogenesis. Titanium surface with anisotropically patterned nanospikes was shown to modulate macrophage polarization and downstream osteoclast differentiation *in vitro* [247]. A nanoporous (30

nm) titanium implant surface suppressed osteoclastogenesis via the integrin β1/FAKpY397/MAPK pathway *in vivo* [248], strongly implicating surface topography effects on precursor cells. In other work, a micro/sub-micro hierarchical titanium surface inhibited the osteoclastogenesis regulatory factor NFATc-1 and reduced the osteoclastogenesis of macrophages *in vivo* [256]. It is interesting to note that the study of surface topography effects in osseointegration - even with respect to the role of macrophages - has specifically focused on osteogenesis and much less focus on osteoclastogenesis. Studies that do exist frequently focus on particle (wear-debris)-induced inflammation leading to osteoclastogenesis [414].

5.3.1.7. The role of T cells in peri-implant osteoclastogenesis.: Both Th1 and Th2 may inhibit osteoclastogenesis by secreting IL-4 and IFN-γ [415]. Th17 cells are osteoclastogenic T helper cell subset. IL-17 from Th17 cells increases osteoclastogenesis *in vivo* by activating NF-κB [416, 417]. T-cells contribute to the release of TNF-α, RANKL, M-CSF, and IL-1, all of which can trigger MSCs and pre-osteoblasts to express RANKL *in vivo* [418] and indirectly support osteoclastogenesis. Importantly, Th17 cells do not induce osteoclastogenesis in the absence of osteoblasts, suggesting that RANKL expressed on Th17 cells alone is not sufficient to induce osteoclastogenesis [419]. Th17 cells also upregulate RANK exhibition on osteoclast precursors [420].

5.3.2. The role of epigenetics in peri-implant osteoclastogenesis—The role of genetics and epigenetics in peri-implant bone loss was recently highlighted [421,422]. Epigenetic mechanisms play a role in osteoblast and osteoclast differentiation, macrophage polarization [423–427], and the modulation of RANKL and OPG expression [423]. Biofilm bacteria may trigger epigenetic changes in peri-implant tissues by binding to TLRs and activating NF-κB and MAPK pathways [428–431]. Epigenetic changes of inflammatory cytokine genes such as IL-1β may lead to excessive peri-implant inflammation and osteoclastogenesis [432–434]. Chronic inflammation may work through persistent signaling that leads to epigenetic changes in the cells of the peri-implant region by suppressing specific transcription factors for osteogenesis or by activating certain transcription factors for osteoclastogenesis [435]. MicroRNAs represent a dynamic epigenetic mechanism around endosseous implants that could participate in the development/progression of peri-implant bone loss. For example, microRNA-regulated pathways control the sequential steps required for osteoclast differentiation [436]. MicroRNAs expressed by peri-implant tissues are related with susceptibility to peri-implant bone resorption [437,438].

There is evidence that bone and immune cell epigenetics are modulated by surface topography [439]. Surface spatial confinement alters the pro-inflammatory functions of macrophages by changing epigenetic profiles *in vitro* [230]. However, little is known about immunomodulation through the surface topography mediated regulation of epigenetic mechanisms in peri-implant tissue resident cells and in immune cells that infiltrate the inflamed peri-implant tissue. Epigenetic mechanisms affecting immune cells (reviewed in Ref. [440]) may be relevant to topography-mediated osseointegration [441] and longer term preclinical (and clinical) investigations are required to reveal these effects.

5.3.3. The relevance of surface topography in immunomodulation of osteoclastogenesis—

The unfavorable and/or destructive osteoimmune microenvironment in systemic conditions such as osteoporosis and diabetes alters the composition of blood and tissue fluids, reduces osteoprogenitor cell recruitment and differentiation; and induces high osteoclast activity, excessive inflammatory responses and compromised M2 macrophage function [269,442]. This negatively affects the formation and maintenance of osseointegration. A hyper-immune status associated with systemic inflammatory disease may negatively influence endosseous implants success by mechanisms involving implant-resident immune cells.

An immunomodulatory implant surface topography may improve osseointegration in compromised conditions by modulating protein-implant interactions and mediating later cellular functions towards the resolution of inflammation, improved bone formation and reduced osteoclastogenesis. For example, a nanostructure titanium design improved osteogenic and angiogenic differentiation and increased the OPG/RANKL ratio *in vitro* leading to improved osseointegration in both diabetic and osteoporotic models *in vivo* [443,444]. A hydrophilic micro-rough surface successfully compensated for the compromised immune function in Type 2 diabetes model by attenuating the pro-inflammatory response and promoting M2 macrophage activity, thus restoring macrophage homeostasis. Proteomic analysis of both surface adherent and wound exudate material showed that this surface promoted an immunomodulatory pro-reparative environment [263]. A biomimetic hierarchical implant surface promoted early osseointegration in osteoporotic rats by suppressing macrophage activation and osteoclastogenesis [256]. The immunomodulatory interactions that occur between implant adherent cells and the alloplastic surface under compromised systemic conditions are still poorly understood and merit further investigation.

5.4. A “Foreign body reaction to titanium implants” theory

Multinucleated giant cells (MNGCs) are a classic identifying feature of the foreign body reaction. They are observed at endosseous implant/tissue interfaces. This is considered a consequence of macrophage activation and chronic inflammation in response to implanted material properties, where high levels of IL-4 and IL-13 are produced leading to fibrous capsule formation [445]. OsteoMacs may be the precursor cell of MNGCs in bone and have been previously reviewed [446]. These multinucleated cells are distinct from osteoclasts as illustrated by differences in surface markers and gene expression profiles *in vitro* [447]. This needs to be further investigated *in vivo* in the peri-implant compartment.

How the monocyte/macrophage lineage differentiate and polarize toward MNGCs has been extensively reviewed [446]. MNGCs are capable of polarizing toward M1 and M2 phenotypes similar to macrophages highlighting their possible role during implant integration and peri-implant bone infection/resolution and there is evidence that MNGCs are associated with increased vascularization and/or new bone formation at bone biomaterials [448]. The macrophage polarization, MNGCs formation and foreign body reaction may be dependent on surface and the surrounding microenvironment characteristics determining the local macrophage activation state. By limiting the action of M1 polarizing factors

in the bone-implant interface and promoting M2 macrophage polarization by biomaterial or pharmacological solutions, it might be possible to limit the osteolysis caused by the inevitably forming foreign body particles. The question of how the multitude of factors secreted by other cells of the implant interface might regulate local foreign body reaction and macrophage polarization and function remains a subject for future studies.

It is suggested that MNGCs may represent a foreign body reaction affecting two important steps in osseointegration: 1) Identification of the titanium foreign body by the immune system, and 2) the development of a bone-forming environment that translates into bone accrual on the titanium surface. This may be interpreted as an attempt to isolate the foreign body from the bone marrow space [449]. An alternative hypothesis is that the MNGCs represent an inflammatory response involving foreign body giant cells [450]. Foreign body giant cells respond to antigens accumulated on the implanted implant surface. This is supported by the relatively sparse localization of multinucleated cells histologically observed along the implant surface. This inflammatory surveillance role directs antigen removal and inflammation leading to osteoclastogenesis and the removal damaged tissue including local bone. This removal of damaged bone is an integral part of the osseointegration process. Invading bacterial pathogens may induce the fusion of macrophages to MNGCs which degrade bone around implants [164,451, 452]. However, MNGCs were shown to be incapable of resorbing bone *in vitro* and have minimal capability to degrade bone compared to osteoclasts with a 40-fold decrease in efficiency [453].

The interpretation of osseointegration as a foreign body reaction driven by MNGCs offers insights and raises questions regarding the cellular processes of osseointegration. However, a classical definition of a foreign body reaction is “an immune-mediated reaction to implanted materials where a cascade of inflammatory events and wound-healing processes result in fibrosis, or the cellular and collagenous deposition that encapsulates implants” [454]. A foreign body reaction follows the acute phase of inflammation, and the continued development of granulation tissue surrounding the implant that contains macrophages, fibroblasts and blood vessels leads to formation of a fibrous encapsulation of the implant separating it from the host tissues [455]. It appears that MNGCs are present at implants, but this does not imply that a foreign body reaction is the driving mechanism for osseointegration. Clearly as this review reveals, other immune cell events at the surface can modulate the osteoinductive and osteogenic events that occur at the interface. While the osseointegration process clearly invokes the function of MNGCs, it also clearly avoids the comprehensive foreign body reaction. This self-limited MNGC response underscores the complex immunomodulatory processes of surface-adherent and localized precursor cells during osseointegration.

6. Concluding remarks

This review provides a summary of the most recent advances in the understanding of immunomodulation in osseointegration and the role of titanium surface topographies for directing progenitor and immune cell fate and function to improve implant osseointegration and prevent bone loss. In the past decade, descriptions of immune cell activities at the implant/tissue interface have illuminated the potential impact of immunomodulation in

osseointegration. However, detailed mechanistic studies are lacking. Further, these studies have clearly revealed the impact of implant surface topography on the reported phenotypes of adherent immune cells. Still, gaps remain in our understanding of topography-related immunomodulatory events at the implant/tissue interface. The interaction of immune cells with MSC/osteoblastic cells and how surface related events influence surrounding bone tissue physiology remain under explored. Current information suggests that surface topography may be useful in controlling tissue responses that reflect immune cell modulation of osteogenic events at alloplastic surfaces. Such tactics and principles are also anticipated to apply to other fields involving alloplastic material/tissue interfaces that address a diversity of biomedical applications. Further understanding of how titanium implant topography influences the population of implant adherent cells has emerged as a fruitful approach to controlling tissue responses at titanium endosseous implant surfaces (Summarized in Fig. 12.)

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The schematic figures are generated using BioRender.

Data availability

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

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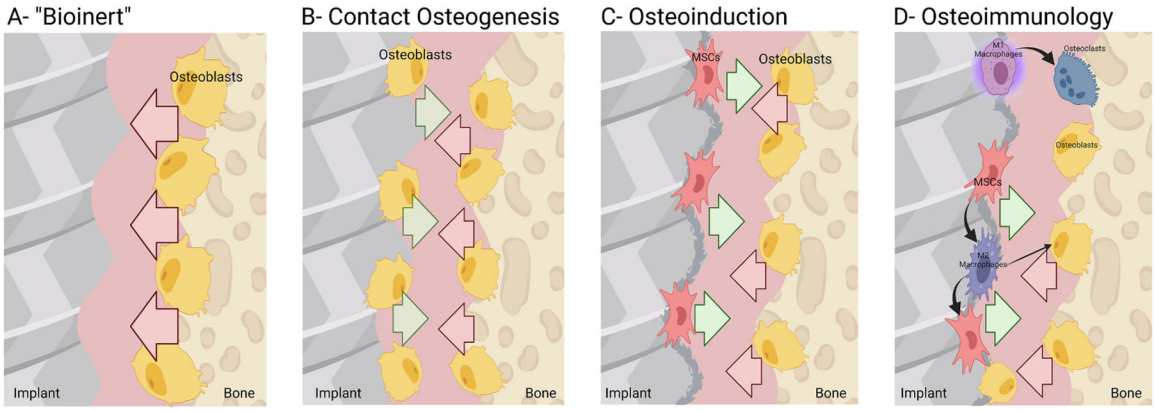

Fig. 1.

Conceptual evolution of osseointegration. Historically, titanium was considered bioinert and osseointegration was viewed as an unimpeded bone formation. The principles advanced for the clinical success of osseointegration were based on the concept that proper bone surgery enabled subsequent formation of bone from the surgical margins toward the implant surface. The attribution of active interactions of the implant surface with adherent cells began with the concept of contact osteogenesis where enhanced surface topography guided the osteoprogenitor cell and their osteogenic functions to the implant surface. Bone formation occurred both from the surface (contact osteogenesis) as well as toward the surface (distance osteogenesis) both accelerating formation of and expanding the bone to implant contact. Continued studies of osteoprogenitor/osteoblast interactions with the implant surface demonstrated that surface topographic modifications were able to increase the rate and extents of osteoblastic differentiation and osteogenesis *in vitro* and were able to increase the bone-to-implant contact at the implant surface in animal and human studies. The osteogenesis-promoting nature of the implant surface was firmly established by studies demonstrating surface-mediated increases in osteoinductive protein and genes expression. This paradigm has most recently shifted to include the concept that the implant surface (principally, but not exclusively, Titanium) is immunomodulatory and bioactive. Investigations clearly demonstrated the presence of other cell types adherent to the implant surface and promoted more recent investigations of implant surface – immune cell interactions. The understanding of osseointegration has evolved to include the role of immune cells in modulating osteogenesis and osteoclastogenesis to affect bone accrual at the endosseous implant interface.

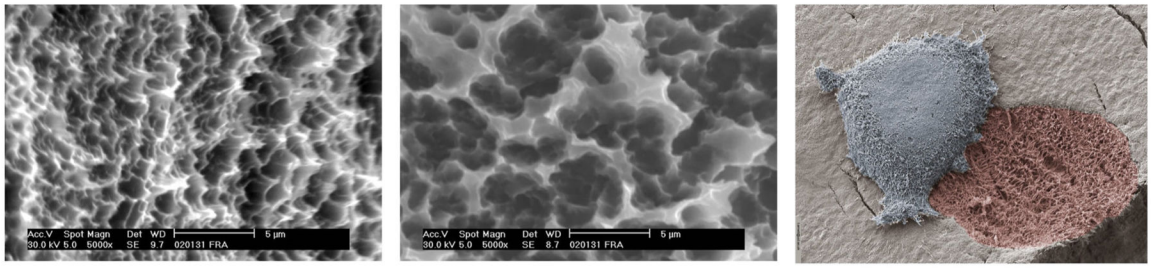

Fig. 2. Topography is a critical variable in titanium surface biomimicry and immunomodulation.

Biologically inspired endosseous implant surfaces mimic the topographical features of an osteoclast resorption pit. Demonstrated are scanning electron micrographs of an osteoclast-resorbed bone surface (right panel) and titanium surfaces that have been acid etched and sandblasted with large-grit corundum. The action of osteoclasts on the bone surface leaves osteoclast resorption pits with microscale, hybrid, and nanoscale textures as well as biochemical cues for MSCs and osteoprogenitor cell recruitment, attachment and differentiation. Current studies suggest that surface topography influences adherent osteoprogenitor cell, immune cell and osteoclastic cell function and their interactions. The physical properties associated with osteoclast resorption pits can be generated on titanium using a variety of techniques, enhancing osseointegration through adsorption of various proteins, recruitment and attachment of pro-healing macrophages, MSCs and osteoprogenitor cells; and osteoblast differentiation, subsequent bone formation and downstream remodeling. The figure for bone resorption pit is adopted by kind permission of Tim Arnett (t.arnett@ucl.ac.uk) & Javier Manzano, from UCL https://boneresearchsociety.org/resources/image/40/#top.

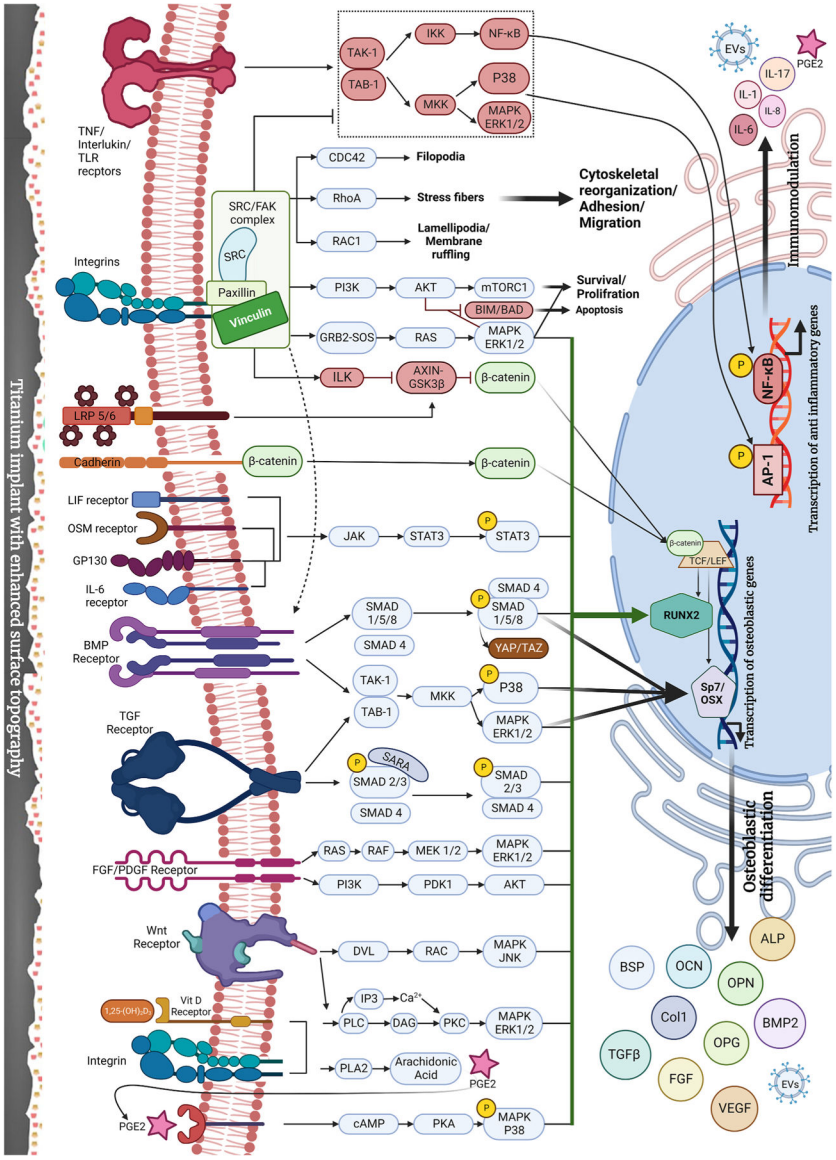

Fig. 3. Signaling pathways activated by titanium surface topography to induce osteoblastic differentiation and decrease the release of inflammatory factors in MSCs.

Surface roughness induces the osteoblastic differentiation of MSCs through multiple pathways. Runx2 and Osterix are major hubs where all osteogenic pathways converge. Surface roughness reduces the release of inflammatory cytokines from MSCs/osteoblasts possibly by blocking NF-κB and MAPK pathways. The detailed description of these pathways are studied in Refs. [60,75,106–108,125].

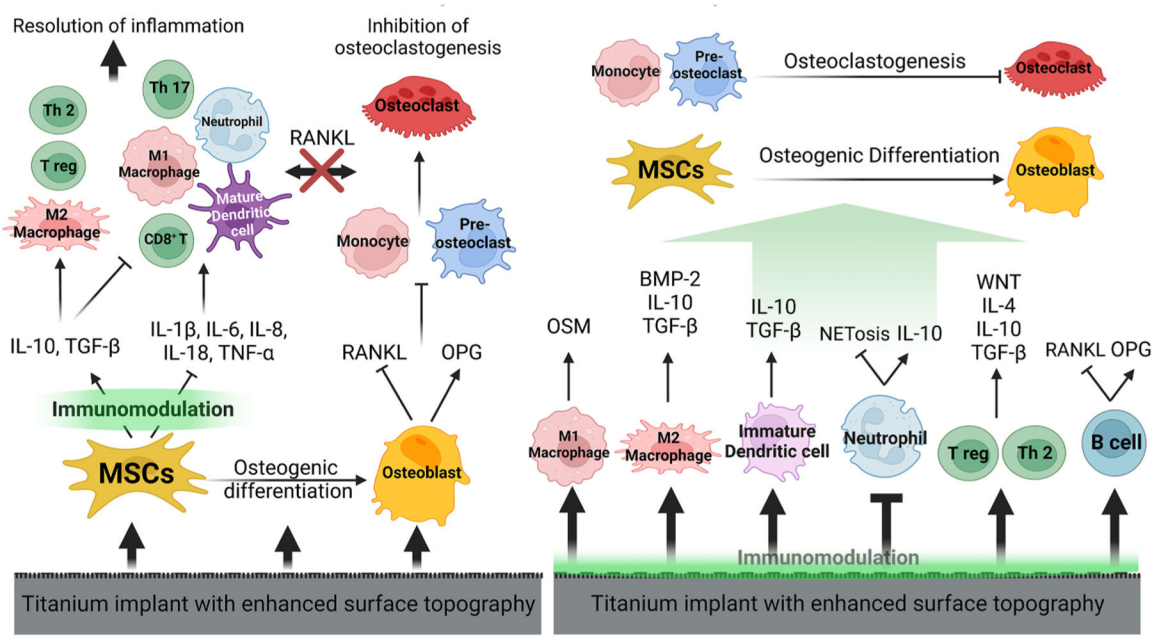

Fig. 4. Immunomodulation in osseointegration; bidirectional regulation of adherent cell function.

The modulation of adherent/adjacent osteoprogenitor cells may represent indirect influence of surface topography that is mediated by adherent immune cells. The cross-talk between immune cells, bone cells and surface topography is discussed in detail in the following sections. The effect of surface topography is shown with arrows arising from the surface.

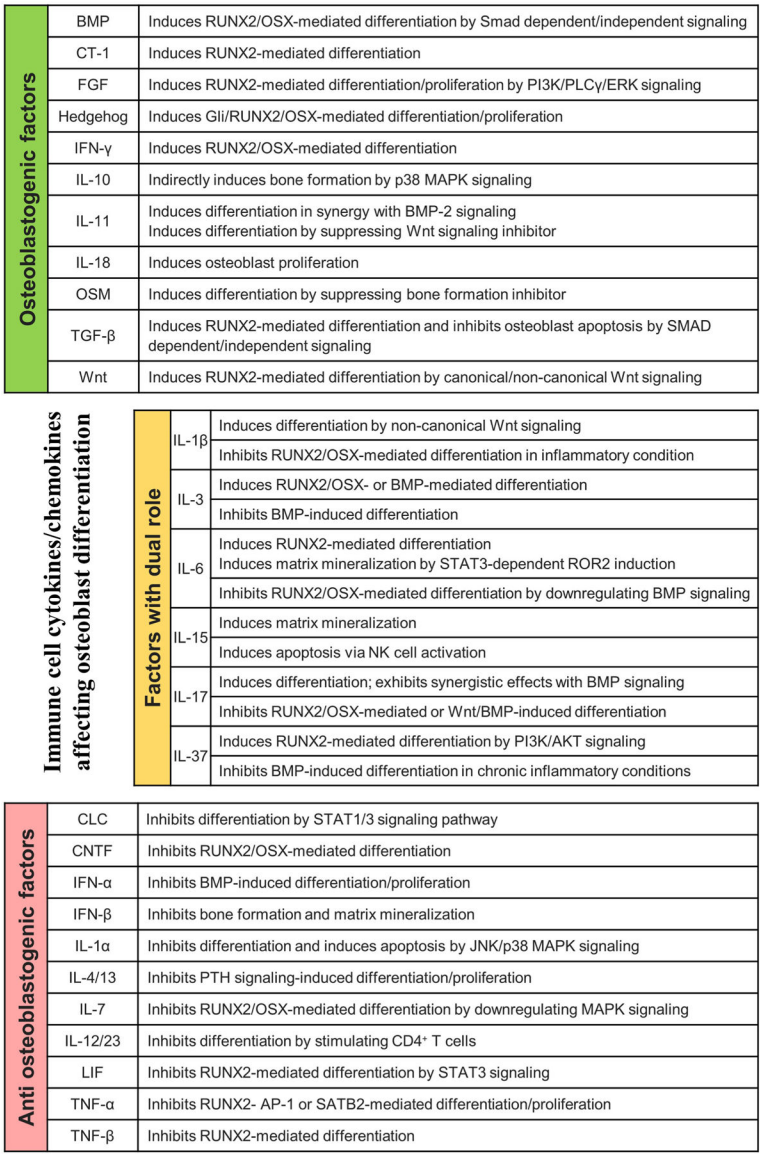

Fig. 5.

Immunomodulation of osteoblast differentiation. A multitude of immune-derived factors promote or hinder osteoblast differentiation and activity.

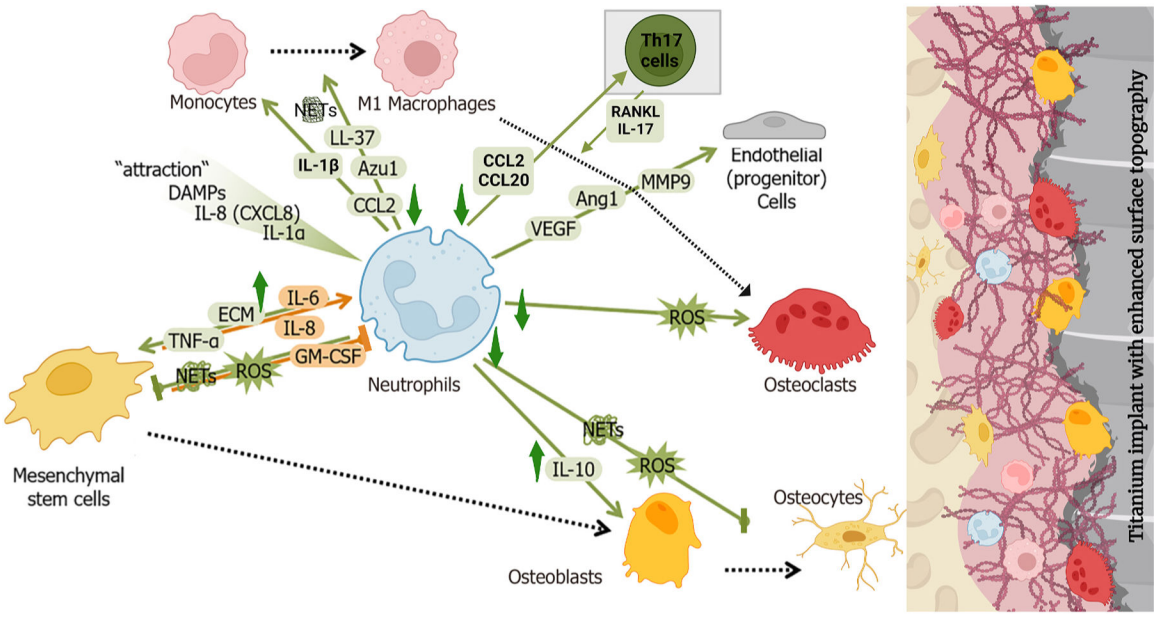

Fig. 6. The possible role of neutrophils in immunomodulation of osseointegration.

Neutrophils may modulate the process of osseointegration by secreting various factors that affect macrophages and T cells activation. An enhanced implant surface topography (rough hydrophilic) decreases NETosis and the release of inflammatory factors from neutrophils and improves osseointegration via downstream signals (dark green arrows). Bone stromal cells secrete factors that regulate neutrophils. Factors secreted from MSCs are depicted in orange arrows and factors secreted from neutrophils are shown in light green arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

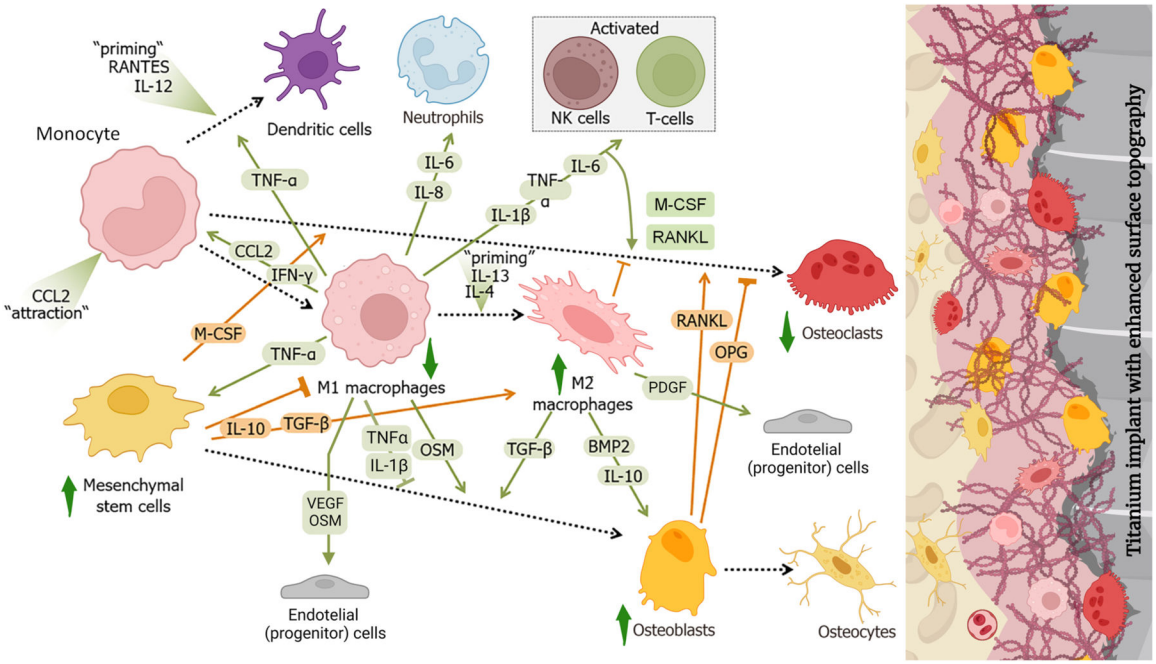

Fig. 7.

The possible role of macrophages in immunomodulation of osseointegration. Macrophages secret various factors that affect osteoprogenitor and other implant adherent cells leading to the resolution of inflammation and improved osteoblastogenesis. The initial M1 macrophage response is independent of surface topography. An enhanced implant surface topography eliminates M1 macrophages and increases M2 macrophages to improve osseointegration via downstream signals (dark green arrows). Both M1 (via OSM) and M2 macrophages (via BMP-2, TGF-β etc.) promote osteoinduction and osteoblast function in bone repair. Bone stromal cells secrete factors that regulate macrophages. Factors secreted from MSCs and osteoblasts are depicted in orange arrows and factors secreted from neutrophils are shown in light green arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

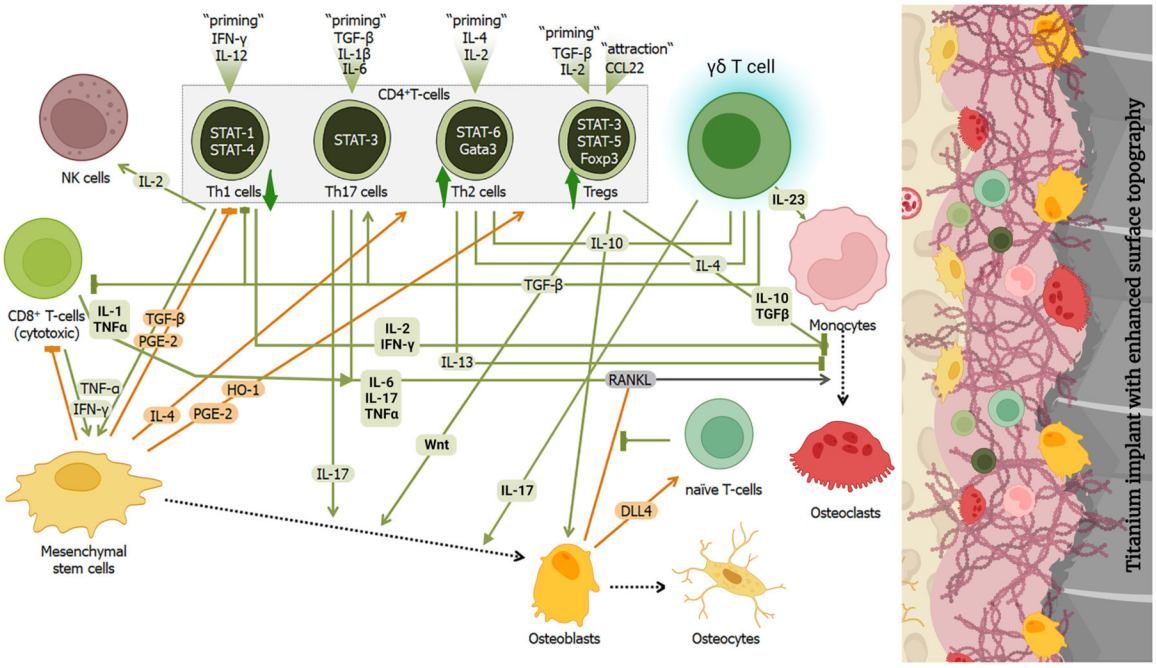

Fig. 8. The possible role of T cells in immunomodulation of osseointegration.

T cells may play roles in the process of osseointegration by secreting various factors that affect osteoblastogenesis and osteoclastogenesis. An enhanced implant surface topography (rough hydrophilic) decreases Th1 cells and increases Th2 and Treg cells leading to the resolution of inflammation and osteoblastic differentiation of MSCs via downstream signals (dark green arrows). Bone stromal cells secrete factors that regulate T cells. Factors secreted from MSCs and osteoblasts are depicted in orange arrows and factors secreted from T cells are shown in light green arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

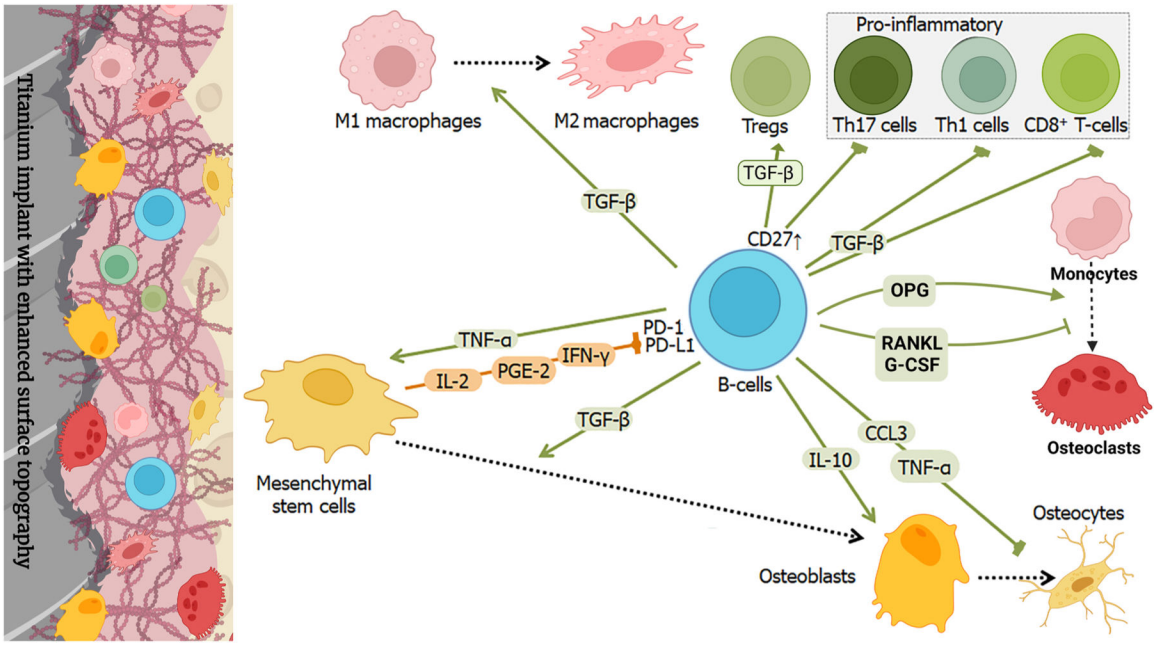

Fig. 9. The possible role of B cells in immunomodulation of osseointegration.

B cells release various factors that affect other immune and bone cells. B cells may participate in the process of osseointegration by secreting OPG and increasing osteoblastogenesis, and increasing M2 macrophage leading to the resolution of inflammation. B cells secrete RANKL during inflammation. The effect of surface topography on B cells is not clear. Factors released from MSCs are depicted in orange arrows and factors secreted from B cells are shown in light green arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

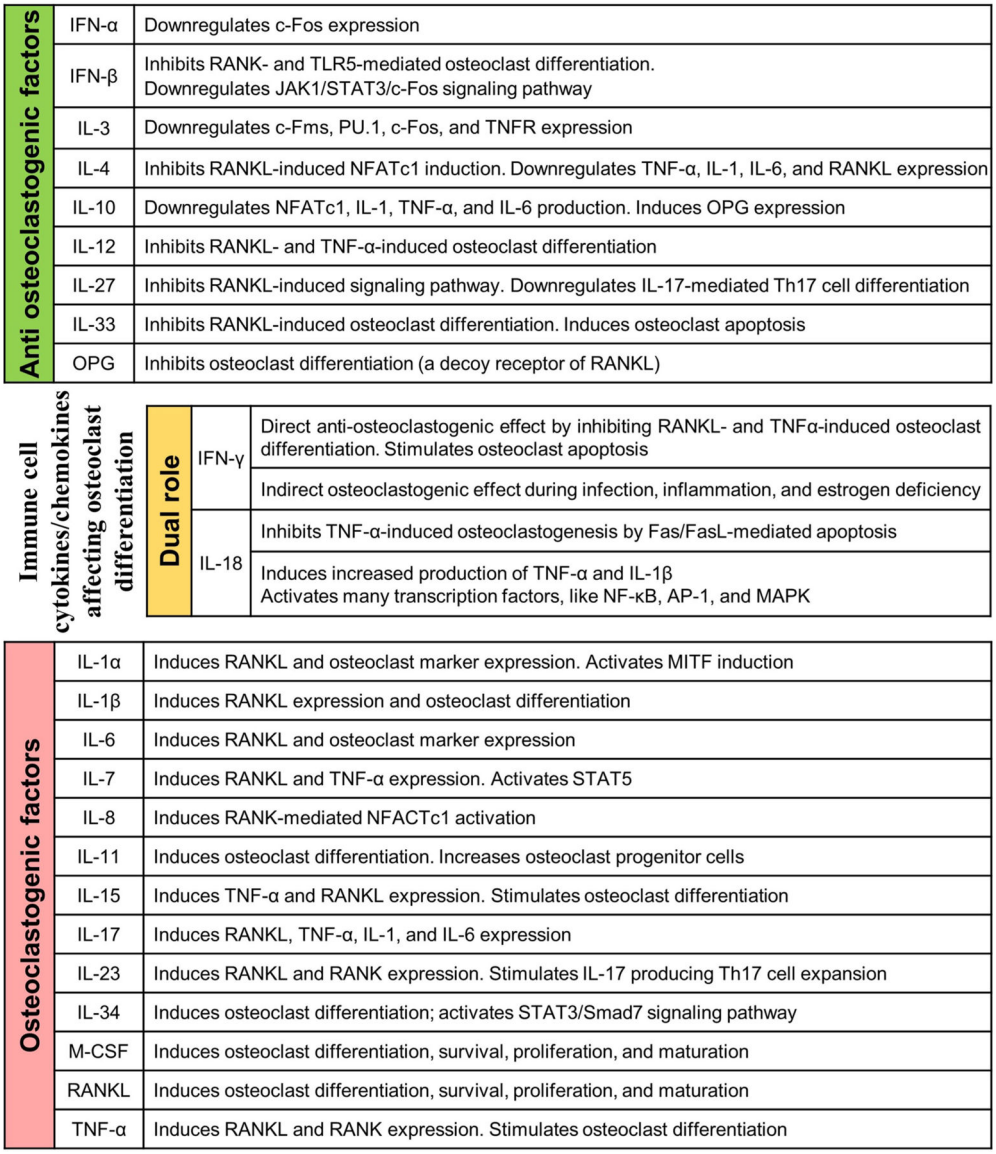

Fig. 10.

Immunomodulation of osteoclastogenesis. Osteoclastogenesis is a complex process as illustrated by the many of immune-derived factors that promote or hinder osteoclast differentiation and activity.

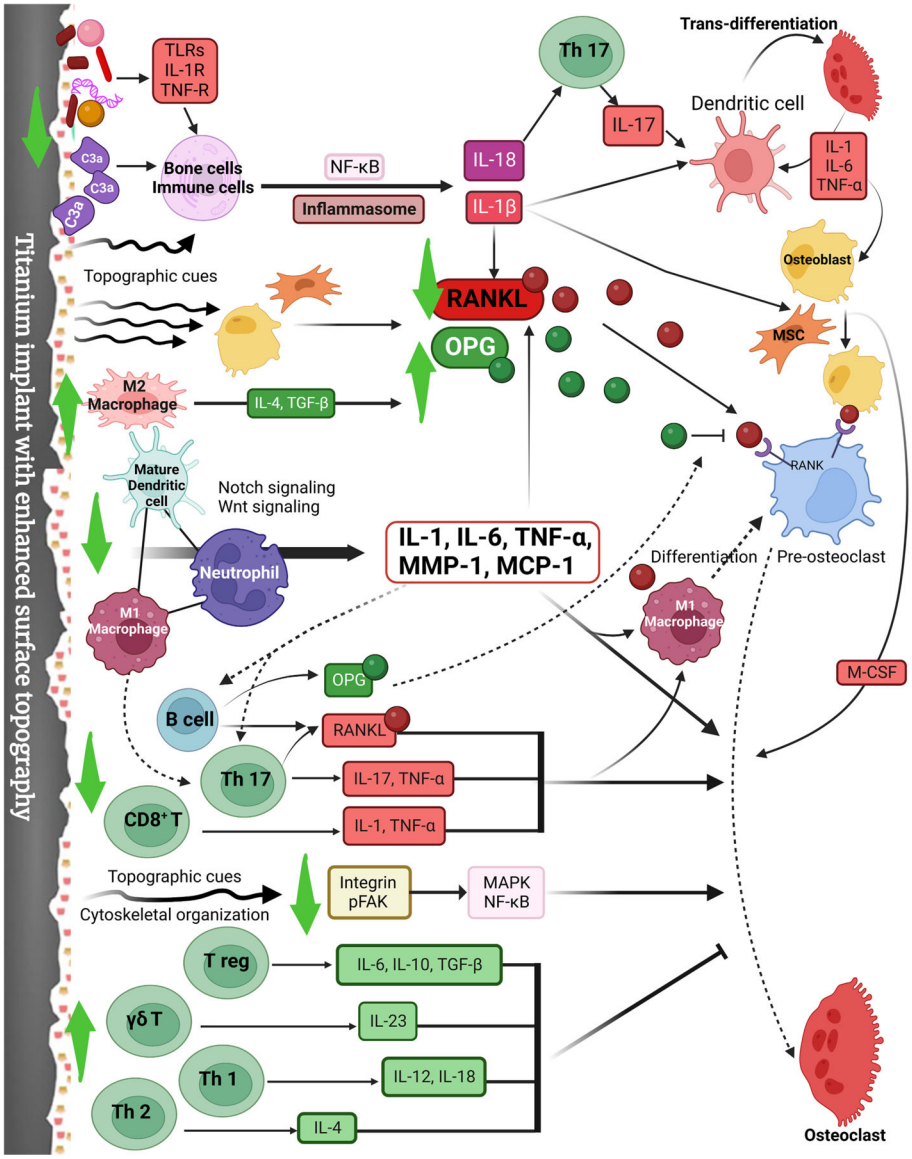

Fig. 11. Immunomodulation of osteoclastogenesis by implant surface topography.

The effect of implant surface topography (thick green arrows) leading to the inhibition of osteoclastogenesis via downstream signals is illustrated. Surface-mediated factors activate inflammasome in various bone and immune cells (osteoblasts, osteoclasts, monocytes, macrophages, neutrophils, and adaptive immune cells, such as T helper 17 cells) leading to the release of IL-1β and IL-18. Elevated IL-1β expression promotes osteoclastogenesis, decreases osteoblast activity, and enhances inflammation by creating a pro-inflammatory milieu in a context- and cell type-dependent manner. IL-1β modulates osteoclast differentiation and activity by direct effects on osteoclasts or by indirectly modulating the expression of RANKL by other cell types. Surface topography can directly activate inflammasome pathway in adherent cells. Topographic cues directly increase OPG and reduce RANKL in bone cells. Increasing OPG/RANKL ratio is central to direct and/or indirect surface mediated anti-osteoclastogenic effects. An enhanced surface topography

decreases the activity of pro-inflammatory immune cells and the subsequent release of osteoclastogenic factors, while inducing the activity of pro-healing immune cells and the release of anti-osteoclastogenic factors. The direct effect of topography to reduce osteoclast differentiation has been demonstrated. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

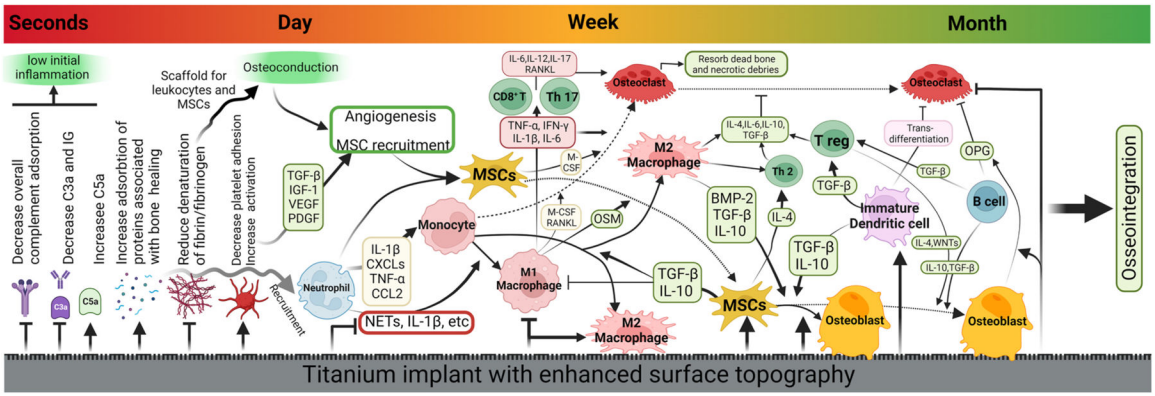

Fig. 12.

Harnessing osteoimmunology and surface topography for modulation of osseointegration. An enhanced titanium surface topography modulates the series of events after implant placement towards the resolution of inflammation and increased osteogenesis. The arrows arising from the surface denote to topographical cues.

Table 1

Summary of the effect of titanium surface topography on immune system components.

	Effect of Surface Topography on Immune System Components[a]			Example References
	Smooth	**Micro-rough**	**Nano-rough**	
Complement system	- Increases C3 and immunoglobulins adsorption - Induces higher inflammation	- Decreases complement adsorption - Induces lower inflammation	- Decreases complement adsorption - Induces lower inflammation	[165]
Platelets	Increases the adhesion of platelets but reduces activation	Reduces platelet adhesion but increases the release of factors that promote bone formation	- Reduces platelet adhesion but increases the release of factors that promote bone formation - Increases blood clot formation	[172,174]
Neutrophils	- Decreases adherence - Increases NET formation - Induces higher levels of proinflammatory cytokines and enzymes	- Hydrophilic micro-rough - Increases adhesion - Decreases NET formation - Decreases the release of pro-inflammatory cytokines and enzymes	- Increases adhesion - Decreases NET formation - Decreases the release of proinflammatory cytokines and enzymes	[151,152, 183–185]
Dendritic cells (DCs)	- Increases DC maturation - Induces higher levels of proinflammatory cytokines and enzymes	- Hydrophilic micro-rough - Decreases DC maturation - Decreases the release of pro-inflammatory cytokines and enzymes	- Decreases DC maturation - Decreases the release of proinflammatory cytokines and enzymes	[153,190, 191]
Macrophages	- Mediates pro-inflammatory polarization - Induces higher levels of proinflammatory cytokines and enzymes	- Mediates both pro- and anti-inflammatory polarization - M2 polarization is enhanced over a small range of micro-roughness - Increases BMP-2 and OSM expression and secretion	- Promotes anti-inflammatory rather than pro-inflammatory phenotypes - Upregulates the expression of M2 markers, BMP-2 and OSM	[215–217, 245,259]
T cells	Increases Th1 and inflammatory population	- Increases Th1 population - Polarizes the adaptive immune response towards a Th2, pro-wound healing phenotype, leading to faster resolution of inflammation	- Decreases Th1 population - Increases Th2 and Treg pro-wound healing population	[154]
B cells	No available date	No available date	No available date	

[a]Refer to the text for detailed description of the involved mechanisms

Table 2

Summary of the effect of titanium surface topography on osteoclastogenesis.

Osteoclastogenic mechanisms	Possible Role of Titanium Surface Micro/Nano Topography[a]	Example Reference
Direct topographical effects	- Mediates osteoclast-implant interactions	[322]
	- Affects cytoskeletal reorganization in osteoclast precursors	[324]
	- Affects the assembly of osteoclast resorption apparatus	[325]
	- Reduces osteoclast activity and inhibit osteoclast differentiation through MAPK signaling pathway	[326,327]
	- Attenuates the osteoclast-induced disruption of osteoblast differentiation by regulating histone methylation	[91]
Indirect topographical effects	- Directs MSCs and osteoblasts to acquire an immunomodulatory role affecting osteoclastogenesis	[105]
	- Modulates the expression of osteoclastogenic factors and OPG/RANKL ratios in peri-implant cells to inhibit the formation of osteoclasts	[24,26,97,98, 329,330]
	- Inhibits osteoclastogenesis via mediation of M2 macrophage polarization	[332]
Inflammasome function	- May influence inflammasome function by reorganizing the actin cytoskeleton in macrophages	[370,371]
NF-κB signaling pathway	- Reduces the activation of early NF-κB transcriptional pathway in macrophages	[256,382]
Toll-like receptors	- Reduces the immune response to toll-like receptors and their expression in implant adherent cells	[256,394, 395]
Complement system	- Reduces C3 activation which induces osteoclast differentiation	[165]
Dendritic cells (DCs) maturation	- Smooth and rough hydrophilic hydrophobic surfaces switch DCs toward maturation phenotypes, increase the expression of pre-inflammatory cytokines and promote osteoclastogenesis.	[153,190]
	- DCs on smooth titanium surface release MCP-1 which induces osteoclastogenesis and the formation of multinucleated osteoclast-like cells from bone marrow precursors	
Macrophage polarization	- Modulates macrophage polarization and downstream osteoclast differentiation.	[247]
	- Suppresses osteoclastogenesis via the integrin β1/FAKpY397/MAPK pathway or inhibiting the regulatory factor NFATc-1	[248,256]
Systemic conditions	- May improve osseointegration by modulating protein-implant interactions and mediating later cellular functions towards the resolution of inflammation and reduced osteoclastogenesis	[256,263, 443,444]

[a] Refer to the text for detailed description of the mechanisms.