Osteoimmunology drives dental implant osseointegration: A new paradigm for implant dentistry

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Abstract

There is a complex interaction between titanium dental implants, bone, and the immune system. Among them, specific immune cells, macrophages play a crucial role in the osseointegration dynamics. Infiltrating macrophages and resident macrophages (osteomacs) contribute to achieving an early pro-regenerative peri-implant environment. Also, multinucleated giant cells (MNGCs) in the bone-implant interface and their polarization ability, maintain a peri-implant immunological balance to preserve osseointegration integrity. However, dental implants can display cumulative levels of antigens (ions, nano and microparticles and bacterial antigens) at the implant–tissue interface activating an immune-inflammatory response. If the inflammation is not resolved or reactivated due to the stress signals and the immunogenicity of elements present, this could lead implants to aseptic loosening, infections, and subsequent bone loss. Therefore, to maintain osseointegration and prevent bone loss of implants, a better understanding of the osteoimmunology of the peri-implant environment would lead to the development of new therapeutic approaches. In this line, depicting osteoimmunological mechanisms, we discuss immunomodulatory strategies to improve and preserve a long-term functional integration between dental implants and the human body.

Scientific field of dental science: implant dentistry.

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1. Introduction

Branemark in the 60s was the first researcher to report bone growing in direct contact with a titanium implant naming it osseointegration. However, osseointegration was more a concept rather than a biological term. Currently, a new paradigm for osseointegration has been proposed, suggesting it as an immune-driven process that leads to new bone formation surrounding the implant surface rather than a pure bone response [1]. Upon this new concept, titanium would activate a tolerogenic balance with peri-implant tissues leading to a foreign body equilibrium (FBE) response [2–4]. Following this, evidence shows that immune response regulates wound/tissue healing and regenerative mechanisms [5]. Findings support the idea that osseointegration could be activated by the same processes during the early stage of peri-implant tissues heal [2,5–7].

Traditionally, osseointegration has been described according to the mechanical stability of titanium implants within bone tissue [8]. On the other hand, myeloimmunology describes the tolerance of the bone marrow microenvironment after the insertion of a tita-
nium implant [9]. Today, novel insights represent the complexity of interactions between both the peri-implant bone niche and bone marrow niche. These interactions include heterogeneous cell populations (immune cells, bone, and vascular cells) [10,11]. The specific interaction between immune and bone cells is called the “osteoinmune system” [12–15]. In turn, osteoimmunology has become a fundamental discipline for the study of several inflammatory diseases, the crosstalk between bone and the immune system, and the influence of the immune system on bone regeneration and consumption [7,16,17].

Briefly, upon titanium dental implant insertion, bone and immune cells interact with a specific protein adsorption pattern that is formed instantly onto the titanium surface, which is critical for modulating the immune response, cell survival, growth, and differentiation [18]. In a recent quantitative polymerase chain reaction (qPCR) and histological study, it was observed that many immune and inflammation related RNA markers adjacent to titanium were up or down regulated at 1–4 weeks of observation, confirming the relationship between immune responses and the formation of osseointegration [3]. These facts lead us to the assumption that the osseointegration of intra-osseous titanium dental implants would depend on an osteoimmunological balance. The concept of osteoimmune balance implies a comprehensive view of the complex harmony of this triad of elements, i.e., bone cells, immune cells, and implants, which finally determines the fate of FBE [3,11,18]. Thus, to improve osseointegration and prevent bone loss of implants, a better understanding of the osteoimmunology of the peri-implant environment would lead to the development of new therapeutic approaches. In this line, several efforts are being developed in the field of immuno modulation to maintain the integrity of FBE in the long term [3,11,19], which will also probably improve the functional integration of the artificial implant-based prosthetic [20].

Growing evidence supports the critical role of the immune system in the modulation of bone homeostasis, healing and repair. However, its role at the peri-implant tissue healing after dental implant insertion remains poorly described. In this narrative review, we summarize new insights in the understanding of how the immune system leads to new bone formation in the peri-implant tissues. We also propose immune-centered therapeutic approaches to improve osseointegration.

2. Immunity and regenerative dynamics in the early peri-implant environment

While fish and amphibians exhibit extensive tissue regeneration, mammals only replicate this property in some specific tissues (e.g., skin and bone) [6,7,21]. Particularly, bone undergoes a genuinely regenerative process after injury, recapitulating embryonic mechanisms [5,22]; however, this inherent capacity of regeneration has a biological limit in humans known as “critical size” [23]. After the implantation procedure, it seems this capacity of bone regeneration is strongly activated, which seems to indicate that titanium implants complement the bone healing process [1,2]. Interestingly, in these biological events both innate and acquired immune mechanisms are required [2,5–7].

Inflammation is the main mechanism of innate immunity and in turn, an initial and tightly controlled inflammatory immune response is critical for bone formation, osseointegration and successful regenerative capacity [5,11,24]. In this initial inflammatory phase, macrophages are widely involved [25], even if the injury is chronic and there is persistent inflammation [26]. Hence today macrophages are considered important to guide the tissue microenvironment at the site of the wound [27]. Macrophages polarize into two phenotypes: the antimicrobial and proinflammatory M1-macrophages, and the anti-inflammatory and pro-regenerative M2-macrophages [28]. An unbalanced M1/M2 ratio with a dominant M1 environment may lead to chronic low-grade inflammation, osteolysis, and loosening of implants [29]. On the other hand, modulation of the M1/M2 balance of macrophages is important in wound healing, regeneration and osseointegration [2,5]. In fact, a balanced M1/M2 macrophage ratio-correlates with M2-associated bone growth at the peri-implant niche at post-implant day (PID) 10 [30,31]. During fracture healing, M2 macrophages participate in both the resolution phase of inflammation and in the homing of mesenchymal stem cells (MSCs) [32,33]. Also, M2 contributes to the ossification phase of fracture repair [34,35]. Surprisingly, for epimorphic regeneration of axolotl limb and zebrafish tail fin regeneration, macrophages also gradually shift to an M2 phenotype during the tissue remodeling stage [6,36]. In addition, it is important to note that a pro-regenerative M2 phenotype can produce trophic molecules, such as Wnt ligands [37,38]; in turn, higher Wnt signaling has been correlated with faster bone healing, faster implant osseointegration [39], a range of functions during embryonic development and organ development [40,41].

On the other hand, the role of the adaptive immune system also seems to be relevant for tissue healing and regeneration [24]. Recent research shows that lower levels of pro-inflammatory cytokines secreted by CD8+ T stimulate the new bone formation by MSC and bone healing [42]. In addition, it is known that CD4+CD25+FOXP3+ regulatory (Treg) cells are essential modulators of the immune response, being able to suppress the inflammatory response and allow reparative processes to stop some forms of autoimmune diseases [5,30]. Interestingly, recent results on bone immune response to titanium implant showed the activation of CD4+ T cells, while the phenotype of CD8+ T cells is suppressed. Therefore, these findings also indicate an adaptive immune response around Titanium [30,31]. Nevertheless, it unknown whether lymphocytes make an acquired immunity participation in the process or if it remains within the innate immunity limits [18].

The role of M macrophages, Tregs, on the activation of osteogenic pathways (i.e.: Wnt/B catenin pathway); strongly suggest that immunomodulatory signals occurred in the early stage of osseointegration recapitulate regenerative mechanisms [2,6,5,7]. However, local immune cell infiltration and macrophage polarization can regulate both bone dynamics [43] and the progression of bone resorption [44], ectopic bone calcification [45] and solid tumors development [36]. Therefore, intermediate stages of M macrophage polarization causing multiples biological scenarios, making the understanding of its role still challenging (Table 1).

3. Immunity: a pivotal player to achieve and maintain osseointegration throughout the implant-bone interface

For an implant become osseointegrated and myelointegrated, it needs to trigger an osteoformative response around the titanium surface at both cortical and cancellous bone levels, respectively [9,46,47]. Cancellous bone is organized in trabeculae surrounded by bone marrow spaces. In turn, the bone marrow is the natural reservoir of MSCs. These cells maintain a stable bone mass and then bone homeostasis through life by differentiating to the osteoblastic lineage, able to secrete bone matrix [13,33,40]. Beside it, MSCs can differentiate into the chondrogenic and adipogenic lineages [3]. Multifactorial inputs, including mechanical stability, aging, and metabolic diseases, will define the fate of these progenitor/stem cells, leading to establishing either an optimal or adverse environment for osseointegration at the bone-implant interface [31,39,48–52].
Besides the stromal component, bone marrow host the hematopoietic cell lineage. Between it, both myeloid and lymphoid progenitor cells give rise to the monocyte–macrophage-osteoclast cell lineage and T cells, respectively [9]. Specifically, bone marrow myelomonocytic cells will support the population of circulant monocytes, which will differentiate into macrophages upon defensive environmental demands [10]. Interestingly, a number of these myelomonocytic cells will give rise to a population of resident or osteal macrophages, named osteomacs, constituting approximately one-sixth of total cell type residing in the bone marrow [53]. Osteomacs participate in bone homeostasis, supporting osteoblast differentiation, function, and bone matrix mineralization [54]. Also, they contribute to bone repair after fracture [43,55].

Regarding the tolerance of biomaterials, osteomacs has been proposed as immune surveillance cells by being in contact with implanted biomaterials [56]. It has been postulated that monocytic-derived cells, possibly osteomacs, arrive at the titanium implant surface differentiating into pro-regenerative M2 and then recruiting osteoprogenitor cells to build the peri-implant new bone [57]. In fact, a macrophage depleted model showed both a reduced number of osteoblasts and less bone formation around implants [58].

Multinucleated giant cells (MNGCs) are fused macrophages contributing to the removal of cell debris after tissue aggressions [59]. Also, MNGCs is associated with foreign body reaction (FBR) and fibrotic encapsulation around biomedical implants [60–62]. Growing evidence from experimental models of oral osseointegration, reported MNGCs at the peri-implant tissues [9,63,64]. This could be related with the adsorbed protein layer on the implant surfaces and macrophages interaction through cell surface receptors called integrins [11,18,65]. In addition, macrophages can bind to a group of endogenous molecules acting as local “danger signals” called damage-associated molecular patterns (DAMPs), which are important for regulate healing outcome [66,67]. In fact, it has been demonstrated that the inhibition of a prototypic DAMPs impaired the osseointegration, causing a higher expression M1 markers and resulting in FBR, with persistence of MNGCs [68]. Interestingly, precursor cells of MNGCs are thought to be derived from osteomacs [56], and in turn osteomacs and osteoclasts (OCs) have a common RANKL-induced macrophage-derived cell line [57,69]. Furthermore, important findings have shown that if the antigen accumulation occurs in surrounding tissues and in the intercellular spaces close to implant surfaces, “it is likely that MNGCs will polarize toward M1–MNGCs, creating an inflammatory environment and probably, their interaction with other cells such as osteoclasts (direct interaction vs. indirect interaction through e.g., T-cells)”. This opens up a whole new field of research, because it has been postulated that they can act as key regulators during peri-implant bone loss [45].

Dental implants are transmucosal devices exposed to oral antigens (i.e., food, bacteria, viruses, fungi, and by their products) during its lifespan [45]. This anatomical feature is associated with the strong immunoreactivity of periodontal tissues [70]. In addition, could be related to the higher T cell co-stimulating capacity of oral Langerhans cells (LCs) phenotype [71]. LCs are dendritic cell (DC) [72], the most potent antigen-presenting cells (APCs) [73,74]. In turn, DCs would participate in the host response against biomaterials raising the inflammatory response [75]. In fact, DCs are critically situated at the osteo–immune interface [73]; however, their roles in implantable devices has been poorly investigated [76], despite there is growing evidence that DCs promoting bone loss by RANKL–activated osteoclasts [77,78]. The primary function of DCs is to present antigens to lymphocytes by the major histo-compatibility complex MHC [79,80], influencing their development and differentiation, to initiate an antigen-specific immune response [81,82]. For the lymphocyte activation, it requires engagement of T cell receptor (TCRs) with MHC/peptide complexes expressed on the surface of DCs, and interestingly, metal ions can interact with these MHC/peptide complexes, like bacterial derived antigens [83].

Free Titanium metal ions can bind to serum proteins and form haptens or hapten-like complexes activating the adaptive immune system driven by a Th1-type response [84–86]. Also, TiO2 nanoparticles can in multiple cell types disrupt epigenetic integrity, through DNA methylation [87]. Furthermore, cobalt alloy particles induce activation of NF-κB, the master inflammatory transcription factor, leading to the release of TNF-α and IL–8 through TLR4-dependent signaling [83]. Cobalt can also modulate the vital and functional parameters of human macrophages, like titanium (TiO2), silica (SiO2) and zirconia (ZrO2) [88]. This is an important issue because the cobalt–chromium alloy is widely used for dental implant suprastructures [89], and there are several potential sources of titanium ions and particles in implant dentistry [90,91]. Besides, organic and inorganic contaminants have been reported on dental implant surfaces [92]. On the other hand, increased levels of metal ions and pro-inflammatory cytokines (i.e.: IL–1β, IL–2, IL–8, IFN–γ, and TNF–α) have been reported in retrieved tissues from aseptically loosened metallic orthopaedic implants [93]. These findings suggest that both the innate and acquired immune response is associated with aseptic metallic implant failure [86].

The above reveals that DCs and macrophages are immunological sentinels present in the peri-implant environment that could determine the lifespan of dental implants [18,45,94]. Moreover, these findings lead us to think that the bone loss around an implant device can occur through aseptic and/or septic osteolysis with similar underlying immune reactions [95]. Therefore, we must be aware of their immune cell capacity when we are planning a dental implant treatment (Fig. 1).

4. Strategies to modulate the peri-implant immune component to achieve and maintain dental implant osseointegration

Functional dental implants are in contact with both hard and soft tissues, through an intraossseous part that reacts with host bone to achieve osseointegration and a transmucosal part, the implant–abutment connection structure that supports prosthetic [96–97]. This special anatomical arrangement predisposes den-
Fig. 1. Hypothetical scenario: Functional dental implant and eventual accumulation of antigens (ions, nano and microparticles and bacterial antigens) with the presence of activated immunological sentinels (DCs and macrophages) throughout the implant-tissue interface. If the inflammation is not resolved or reactive due to the stress signals and the immunogenicity of the elements present, there is a risk that initially relatively harmless peri-implant bone loss progresses to a more damaging and vicious stage, due to the polarization capacity of the MNGC. Ag = antigen; DC = dendritic cell; F = fibroblast; HBMMSC = human mesenchymal stem cells derived from bone marrow; L = lymphocyte; M1 = macrophage; MNGCs = multinucleated giant cells; Ob = osteoblast; Oc = osteoclast; Ost = osteocyte.

Fig. 2. Immunomodulation strategies to improve, maintain and eventually recover osseointegration: A) Modification of implant surfaces properties may improve osseointegration, probably by switching the phenotype of peri-implant macrophages from the pro-inflammatory (M1) subset to a pro-regenerative one (M2). B) Osseointegration needs to be maintained, this could be possible by reducing an eventual secretion of pro-inflammatory cytokines through ionic-treated implant surfaces with LiCl or Mg. C) Another approach is centered on the modulation of macrophage phenotype using polarizing cytokines such IL-4. D) Recently, it has been proposed that an external mechanical stimulus directed to the peri-implant tissue could promote the innate immunomodulatory capacities of BMMSCs, influencing CD8 and macrophages, ths through mechanosignal transduction and the release of exosomes (ex). Ag = antigen; Ex = exosome; HBMMSC = human mesenchymal stem cells derived from bone marrow; M2 = macrophage; MNGCs = multinucleated giant cells; Ob = osteoblast; Oc = osteoclast; Ost = osteocyte; Tol-DC = tolerogenic dendritic cell.

tal implants to several factors from the local oral environment: implant overloading, periodontal infection, cement, and metallic debris or ions released from the implant components [98]. In addition, in the presence of metallic ions, such as impurities or alloys like Co and Ni, the anatase–rutile phase transformation takes place even at normal conditions, that would alter the biological characteristics of a TiO2 surface [99]. Thus, oral implants can be exposed to various clinical factors, however, also many factors associated with the patient. Certain genetic polymorphisms of cytokines such as interleukin (IL)-1b, habits such as smoking and alcohol consumption, the intake of medication for certain diseases, are thought to influence the host response [18]. But even more importantly, these factors (clinical and patients) together may trigger the immune system to a different reaction possibly resulting in implant rejection [100]. In general, when a device is implanted, within either soft or hard tissue, the material surface adsorbs proteins from blood initiating the inflammation cascade mediated by the innate immune system [101]. However, if the inflammation is not resolved or reactivated due to the stress signals and the immunogenicity of elements present, there is a risk of implant
failure [100,102,103]. Fortunately, there is evidence that immune response during biomaterial-mediated osteogenesis can be manipulated through beneficial “osteoinmunomodulation” [82] (Fig. 2).

Modifying material properties may decrease the immune response to implanted biomaterial [102]. In this sense, it is known that the modification of implant surfaces with titanium oxide (TiO2) nanotubes positively affect the osseointegration, probably by switching the phenotype of peri-implant macrophages from the pro-inflammatory (M1) subset to a pro-regenerative one (M2) [104–109] (Fig. 2A). The immunomodulatory capability to promote pro-regenerative macrophage polarization, through additive manufacturing (AM) porous titanium, has also been studied [110]. Furthermore, the use of hydrophilic surfaces appears to be able to influence macrophages to produce an anti-inflammatory microenvironment [111]. These surface modifications are a critical approach to induce osteogenesis for the next-generation of intraosseous implants [104]. However, the main studies analyzing the osteomunomunological response around dental implants consider c.p. titanium implants [2,30,31]. Therefore, there is still a lack of knowledge about the osteomunomunological response upon implant surface modifications such sandblasted/acid-etched (SAE) [111].

Attaining the FBE-mediated osseointegration, it needs to be maintained during the lifespan of a loaded implant. Biologically, the interplay between bone cells, immune cells, and implant surface would determine the fate of FBE [11,12]. Thus, ionic-treated implant surfaces would modulate a pro-regenerative immune response and then optimizing osseointegration. For example, high concentrations of magnesium (Mg) in the implant surface reduce the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and PEG2 [113]. A recent study highlights the immunomodulatory effect of lithium chloride (LiCl) by mitigating the macrophage-driven periprosthetic inflammation in particle-induced osteolysis models [114] (Fig. 2B). Another approach is centered on the modulation of macrophage phenotype using polarizing cytokines [112]. Indeed, macrophages can be activated to the anti-inflammatory M2 phenotype by the exogenous addition of polarizing cytokines IL-4, IL-13, or IL-10 [115]. Therefore, adding IL-4, the macrophage phenotype polarizes from the pro-inflammatory (M1) to the tissue regenerative (M2), leading to a pro-osteogenic response. This transition from M1 to M2 has been associated with an increase in bone anabolic factors CCL2/MCP-1, CCL5/RANTES, and IGF-1 in vitro [116] (Fig. 2C).

On the other hand, MSCs represent one of the most promising tools in regenerative medicine, thanks to their potential for proliferation, differentiation, and their innate immunomodulatory capabilities [112,117]. In this line, MSCs influence not only T cells but also other cells of the immune system, such as DCs and macrophages [118]. Interestingly, bone marrow-derived MSCs (BM-MSCs) modulate the immune response through a series of mechanisms, among these the generation of tolerogenic DCs (Tol-DCs) [119]. Current evidence indicates that BM-MSCs can modulate the immune response by inhibiting polarization induced to M1 macrophages and promoting polarization to M2 macrophages through the release of paracrine factors [120]. Hence, local BM-MSCs could immunomodulate the local response in favor of osseointegration [121]. Furthermore, studies about the mechanobiology of stem cells, have shown that mechanical stimuli induced signaling pathways that play essential roles in cellular differentiation and the determination of stem cells’ fate (mechanotransduction) [122–124]. Interestingly, there are sensory organelles called primary cilia that play a critical role in mechanotransduction and BM-MSCs do indeed possess these organelles [125]. A recent study has confirmed the importance of these organelles in MSC biology. Thus, stem cell mechanotransduction could be targeted therapeutically [126]. Mechanosignaling also affect the phenotype of immune cells, such as macrophage and dendritic cells [127,128] and is a potent pathway to counteract inflammation activated by the NF-κB signaling cascade [129]. In this line, osseointegration was associated with mechanotransduction to maintain FBE in the long term [11,121] (Fig. 2D).

5. Functional integration of dental implants after achieving the immune equilibrium

Despite the inherent complexity of the peri-implant environment, oral implants have developed rapidly, and their development has shifted mainly toward esthetics and simplified use [130]. However, the importance of the peri-implant osteoinmunology [68] and the neurophysiological integration of dental implants remain only partially understood [131]. In relation to the latter, new evidence relates tooth loss with the increased risk of diminished cognitive function [132] and in turn it is thought that dental implants may play a role in maintaining cognitive function [133]. Moreover, it has been demonstrated that dental implants activate cortical somatosensory areas [134], and osseointegration increases over time [135].

It has been suggested that the extent of bone apposition to the implant might be of importance in the grade of osseointegration. In fact, it has been demonstrated that implants with a SAE surface have high bone to implant contact and are more sensitive than machined implants [136,137]. Interestingly, it is known that nerves in bone can interact with bone cells [138] and regenerative paradigms exhibit nerve dependency [139]. It is for this reason that the use of neurotrophins (e.g., nerve growth factor (NGF)) has been proposed in dental implants, because NGF is related to the survival of peripheral sensory neurons [140] and bone formation after bone fracture [141]. Hence, the use of suitable methods to induce peri-implant nerve regeneration could be effective for improving proprioception of dental implants [142]. In addition, recent findings have related the polarization of M2 macrophages with the restoration of axonal regeneration [143], proving the functional links between the immune system and the nervous system [144]. Surprisingly, there is an M2 regulation in the peri-implant environment [2,31,111] and both neurofilament-positive fibers and nerve bundles have been observed near the titanium implant surface [63,145]. Furthermore, it has been demonstrated that nerves retain a degree of physiological function suitable for creating an osseointegrated neural interface [146]. Nevertheless, the role of this peri-implant innervation remains only partially understood [131].

Evidence of osseointegration shows that an appropriate peripheral feedback pathway can be restored with the use of osseointegrated implants [147]. Thereby, the restoration of the somatosensory control loops would allow the patient to live a normal life with a prosthesis and reduce the risk of overloading artificial prosthetic and/or implants [136]. Hence, from the psycho-physiological point of view, a better understanding of the complex human interaction with implantable devices is necessary [148]. But at the same time, it is necessary a reliable and long-term stable host–implant relationship [149] which would not be possible if the FBE were to be compromised [4,18]. Therein lies the importance of understanding host osteoinmunology and the development of peri-implant immunomodulation strategies [11].

6. Conclusion

1. It is suggested that titanium dental implant induces a critical pro-regenerative environment in the early stage of osseointegration.
2. It seems that osteomacs and dendritic cells are immunological sentinel highlights present in the implant–tissue interface, being able to activate a T cell-mediated response.
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