Current Concepts for the Biological Basis of Dental Implants

Foreign Body Equilibrium and Osseointegration Dynamics

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KEYWORDS

• Implants • Osseointegration • Foreign body reaction

KEY POINTS

- Bone as a complex and multifunctional tissue is an important factor in osseointegration.
- Implant protein adsorption and the immune system are key determinants.
- Foreign body equilibrium involves osseointegration and implant foreign bodies.
- Osseointegration is a dynamic process results from a complex set of reactions.
- Several host mechanisms and pathways interact to allow the integration of the implant in the host tissues, namely bone and oral mucosa.

INTRODUCTION

It has long been established that successful osseointegration, with direct bone apposition onto the surface of the implant,[1] is the 1 key event that allows millions of implants to successfully help in replacing inevitably lost teeth every year.

One must have an individualistic approach to patients in need of implants, if biology is to be considered; the genetic basis of individuals plays a more important role than might be perceived initially, which has been demonstrated by studies that link early periimplant marginal bone loss to certain genetic polymorphisms of cytokines such as interleukin (IL)-1β,[2,3] whereas habits such as smoking and alcohol consumption, or the intake of medicines for certain diseases, are thought to have an effect on the human body mechanisms that guide the dental implant–host relationship.

Upon insertion, implanted materials are coated rapidly with blood and interstitial fluids' proteins that get adsorbed onto the surface; 1 hypothesis is that it is to this adsorbed layer that cells primarily respond and not to the surface itself, although it is clear that such cell surface interaction is pivotal for cell survival, growth, and differentiation.[4]

Clearly, the importance of the pristine surface is substantial because one particular surface may produce a severely different effect on host proteins when compared with another surface, which may in turn result in a profound difference regarding the subsequent tissue formation around the implant.

The immune system, previously overlooked by many researchers, is believed to play a decisive role in the biological mechanisms that determine the fate of any implant placed within living tissues.[5,6] This means an important shift in paradigm is taking place, where biomaterials are perceived

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as immunomodulatory rather than inert bodies, with huge consequences for implant dentistry and other biomedical applications.

The focus is currently changing regarding how host molecules and cells first interact through complex mechanisms when reacting to an invading foreign entity with particular chemistry, surface characteristics (that might have been manipulated or not in an attempt to achieve an improved outcome), and macroscopic design for favorable load distribution. All such factors play an essential role on the immediate and long-term success of osseointegration at the cellular level and is explored in this article.

TISSUE CHARACTERISTICS

To understand the biological basis of osseointegration, one has to understand the 2 main sides of the implant–host interaction: the tissue characteristics and the biomaterial characteristics. This article addresses the osseous tissue characteristics, as well as the potential role of soft tissues in dental implant's osseointegration.

Bone as an Immune and Endocrine Organ

The bone marrow is known to be a hematopoietic organ. Some authors also consider bone as an immunity regulatory organ, given the presence of dendritic cells (DCs), regulatory and conventional T cells, B cells, neutrophils, and mesenchymal stem cells, which elicit a role in regulating body wide immune reactions.[7]

Furthermore, besides being the target of hormones, bone also seems to function as an endocrine organ, as recent evidence suggests that 2 bone-derived factors can work as hormones:

a. Fibroblast growth factor 23 is produced by osteocytes in bone and inhibits hydroxylation of vitamin D and promotes phosphorous excretion in the kidney
b. Osteocalcin, a frequently assayed mediator in osseointegration studies, is also considered a hormone produced by bone osteoblasts acting distantly on pancreatic β cells to stimulate insulin production, on muscle cells inducing glucose uptake and on adipocytes to increase adiponectin production.[8]

Therefore, bone is a complex living tissue:

a. With its calcium homeostasis function
b. Functioning as an organ with the responsibility of producing hematopoietic cell lineages
c. Populated by immune cells that regulate inflammation and the immune system
d. Has an endocrine function through the production of mediators that work not only in a paracrine fashion, but that in reality are hormones that have an effect on distant organs and tissues.

Hence, bone-born implants are placed in a complex tissue (many functions of which were unknown until recently) that can be affected potentially by certain implant material characteristics. Osseointegration of implant devices may also be affected potentially by these cells and mediators that populate the osseous tissue.

Bone Cells

Bone remodeling results primarily from the coupled function of 2 of the bone cells, which are interdependent:

a. Osteoblasts (bone-forming cells)
b. Osteoclasts (bone-resorbing cells).

Another important notion is the organization of these cells in basic multicellular units (BMU), which perform the remodeling task.[9] The fine balance between bone formation and bone resorption is controlled by an intricate web of pathways that act on and from the BMU; depending on the stimuli, the result will be either bone growth or loss. Regulation of bone homeostasis and remodeling is known to also involve immune cells, such as B and T lymphocytes, whereas cells known as osteomacs (macrophages present in the bone in close connection with osteoblasts) have been demonstrated, in vitro and in vivo, to regulate the osteoblastic mineralization activity.[9] From an osseointegration point of view, the role of BMUs in a biomaterial context has not yet been entirely understood.

Further studies are also needed on how different stimuli, such as certain drugs, diseases, or local strains from an implant may affect the BMU, and how this may prevent the desired bone quantity and quality and thus hinder the successful clinical application of an implant.[10]

As for the remaining bone cell type, osteocytes, a recent publication has reported on the direct contact between these cells' dendrites and the implant surface, after an 8-week osseointegration period in an in vivo model. From this viewpoint, and considering that osteocytes are important cell homeostasis regulators and may act as mechanosensors, further studies are needed regarding the role of these cells in long term osseointegration maintenance.[11]

Cellular and Molecular Basis of Osseointegration

Osseointegration is a dynamic process that results from a complex set of reactions, where several

host mechanisms and pathways interact to allow the integration of the implant in the host tissues, namely bone and oral mucosa. Once the implant material is perceived in the described biological context, it is easier to understand the reactions that potentially take place at the implant–tissue interface.

In implant dentistry, the literature has focused over the years on describing osseointegration from a purely wound healing point of view. Material science, nevertheless, has been describing the participation of the immune system in the relationship of biomaterials with host tissues for a few decades now. There is no doubt that the successful integration of implants, regardless of tissue type, is driven by inflammatory processes. In fact, without inflammation, integration in the tissues may not even take place. To correctly understand the osseointegration of dental implants, a deeply embedded concept must be challenged. In dental implant science, titanium and other materials being applied for the same purposes have so far been considered inert. However, some authors currently consider that implant materials, be those intraoral or extraoral implants, orthopedic implants or even bone substitutes, may instead be immunomodulatory.[12]

This change in concept raises 2 questions:

a. If a material is capable of modulating the immune system, what consequences may be expected?
b. In what manner is the immune system important to the bone and even the soft tissue response to dental implants?

First, biomaterials are unlikely to be inert when in contact with living tissues. This is because proteins are adsorbed instantly onto the surfaces of all foreign materials once these are implanted.[13] Protein adsorption is the first key for tissue integration with biomaterials, and this physicochemical property is set to influence the ensuing group of reactions, modulating the host response in its entirety. Protein adsorption consists, in general terms, of the unfolding of local host proteins when in contact with the biomaterial surface. This conformational change results in the exposure of potentially biologically active peptide units (epitopes) that can trigger a different set of host molecular and cellular responses, when compared with a situation where a biomaterial is absent.[14] Such resulting set of reactions may be beneficial or not to the patient.

Eaton and Tang and colleagues have worked on the relationship of protein adsorption with biomaterial integration and in 1 study found that fibrinogen, a known important glucoprotein at surface interaction, behaves differently when adsorbed or denatured, when compared with the nonadsorbed, soluble form. Once adsorbed, fibrinogen exposes 2 previously hidden amino acid sequences P1 and P2, that function as epitopes and bind to phagocyte's integrin Mac-1 (CD11b/CD18) leading to a proinflammatory environment and modulating the host response to the biomaterial. Thrombin-mediated conversion of fibrinogen to fibrin also exposes the P1 and P2 epitopes, with similar consequences,[15] eliciting the participation of thrombotic events in the implant osseointegration events.

Protein adsorption is intimately related to the surface characteristics of the material, a feature that has been studied extensively. Surface topography, for instance, is known to be fundamental for improved osteoconduction of implant biomaterials,[16] playing a crucial role in the complex bone–implant interface reactions both at the microstructure and nanostructure levels.[17] Osseointegration of titanium implants depends on the cellular response to surface modifications and coatings,[18] which is intimately related with the protein adsorption pattern.[19]

Studies have focused mostly on the ability of the proteins adsorbed to promote the adhesion of osteoblasts,[20,21] and some authors have extended their interpretation to the benefit of avoiding the attachment of bacteria, in a so-called selective protein adsorption[22] through a process that avoids the adsorption of nonspecific proteins, affording a nonfouling surface to titanium, although it is not clear if such change of surface chemistry with peptides will negatively interfere with osseointegration.

Other studies have used implants coated with key proteins (eg, fibrinogen), assessing the biological response,[23,24] when compared with uncoated implants.

a. Fibrinogen seems to have a beneficial effect on tissue integration
b. Bougas and colleagues[25] have demonstrated in vitro that laminin induces a higher CaP deposition on the implant surfaces, even though the in vivo performance at the early osseointegration period was difficult to demonstrate at this initial stage of research. Q9

Such mechanisms are yet to be understood and protein adsorption remains a controversial topic, especially when considering that it might be beneficial in some biomedical applications, whereas for others it could be detrimental (friend or foe?).

The doubts surrounding protein adsorption are:

a. Identifying the key proteins in the process
b. Whether some are unwanted
c. And especially to what extent should a protein unfold, because different degrees of linear conformation could possibly expose different peptide units, ending up in potentially different outcomes, some not necessarily beneficial for the implant integration with the tissues.

Evidently, more emphasis and importance is placed by the current text authors on the chemical and signaling ability of the protein adsorption phenomenon, although this cell adhesion facilitation is not discarded. In such a context, it is understood that the adsorption event is likely to influence the local immune response, by modulating the immune system components in reacting in a certain way. This process is what was referred to as immunomodulation.

IMMUNE SYSTEM AND TISSUE INTEGRATION

The immune system is thought to play a crucial role in biomaterial integration in host living tissues.

Several mechanisms are to be considered:

a. The normal healing mechanisms in response to the trauma caused by the surgical implant procedure that involve different cellular and molecular mechanisms, such as the coagulation system, the kinin system, platelets, fibroblasts, osteoblasts, and mesenchymal stem cells, among others[26]
b. An immune response that runs not only in parallel, but also interacting with the mechanisms in point (a), resulting in a complex network of reactions that dictate the long-term fate of the implant.[27]

It is believed that the host reaction to implants is regulated by innate immunity (the human body's nonspecific defense mechanisms, performed by the complement system, monocyte-macrophage cell lineages and B1-type lymphocytes),[6,28,29] although adaptive immunity (antigen-specific defense mechanisms, mediated by B or T lymphocytes) might also play a role in such a process.[30] After the protein adsorption phenomenon, the complement system is activated[5] and macrophages guide the inflammatory response to the biomaterial.[6]

Complement System

The complement system is part of the innate (nonspecific) immunity. It is composed by several plasma and cell membrane proteins that have the important task of distinguishing "self" from "nonself" entities, including foreign bodies,[31] participating in the direct or indirect (through activation of immune cells) elimination of threats to the human body.

Studies on biomaterials that are in direct contact with whole blood have reported on the role of the complement system, through its different known pathways, in guiding the host reaction to such biomedical applications.[31,32] Beside immune cells, like macrophages and lymphocytes, complement factors are also known to interact with osteoblasts under certain conditions, while also being able to induce osteoclastogenesis.[6] The complement system may, thus, have an important role in mediating implant–host interactions, such as the one leading to osseointegration.

Macrophages

Macrophages represent another important key in the osseointegration process. Macrophages are considered the sentry cells of the immune system; they work as a traffic roundabout where all immunologic and inflammatory reactions are controlled and guided.[29,30] This process is not understood entirely, but that is the center of attention for a considerable number of researchers integrating teams that focus on all aspects of health-related topics, including oncology, nutrition, atherosclerosis, and autoimmune diseases. They are also being studied and applied in cell therapy for the treatment of some diseases.[29]

Macrophages play an important role in the inflammatory balance, because they can assume rather different phenotypes that depend on local conditions:

a. M1 macrophages present the classical phagocytic and proinflammatory characteristics
b. M2 macrophages are involved in tissue repair and healing.[33]

Even more interesting is the versatility of macrophages, which adapt their phenotype to changes in the local environment.[6]

The role of macrophages in osseointegration is greater than previously expected. Basically, although neutrophils are recruited on the basis of a pure wound healing phenomena, macrophages are only recruited if a biomaterial is present[27]; when in the presence of foreign entities, macrophages further fuse into foreign body giant cells that are multinucleated giant cells formed to deal with larger targets.[34] These cells are found frequently on the surface of titanium oral implants[35] and justify the concept of osseointegration being a foreign body reaction,[5,6] because

oral implants are in themselves foreign bodies. This concept was early realized by the German pathologist Karl Donath, who suggested such concept in a work published in 1992.[36]

Albrektsson and colleagues[5] introduced the concept of foreign body equilibrium:

a. Osseointegration is the result of a foreign body reaction that, with the right intensity in the inflammatory response, will balance itself out and allow for bone to grow on the implant surface
b. Similar to soft tissue implants, which end up encapsulated in poorly enervated and vascularized fibrous tissue, dental implants also become surrounded by condensed bone that is very poor in vascularization and enervation, the typical result of a foreign body reaction that has reached equilibrium[5]
c. The ongrown bone may be seen as a manner of shielding off the foreign entity from the tissues, that is, as a protective mechanism.

Lymphocytes

Lymphocytes interact with macrophages and also with bone cells, thus eliciting their participation in the osseointegration process.[12] The question is whether lymphocytes render an acquired immunity participation in the process or if it stays within the innate immunity boundaries. We also need to clarify whether these cells play a role in the buildup process that result in osseointegration or if only activated during the pathologic breakdown of osseointegration, leading to marginal bone loss.[6]

Marginal Bone Loss

In the same context, periimplant bone loss is the result of the immunologically led loss of the inflammatory balance. This concept is reinforced by the fact that osteoclasts, which are bone resorbing cells, can result from the fusion of macrophages[6,37]; however, some authors suggest that macrophages are themselves able to perform bone resorption.[38] It is not clear whether the bone loss seen and described as periimplantitis by Albrektsson and Isidor in 1994[39] is the result of bacterial colonization through the implant surrounding mucosa, despite this being the currently accepted theory in implant dentistry.

The mechanisms involved in such pathologic finding, for example, receptor activator nuclear factor-κB ligand (RANKL, which promotes macrophage fusion into foreign body giant cells and osteoclasts)[37] are also expressed in inflammatory pathologic conditions that do not result from infection, such as autoimmune diseases like rheumatoid arthritis[40] and in what is described in orthopedics as aseptic loosening,[41] where periimplant bone loss occurs in the absence of bacteria.

Marginal bone loss around oral implants is related to the implant type, clinical handling, and patient characteristics,[42] a trilogy that is difficult to couple to a disease such as periodontitis around teeth. The start of marginal bone loss around oral implants depends on disturbance of the foreign body equilibrium owing to the trilogy of factors and is characterized by recruitment of bone resorbing cells and gradual disappearance of bony support around implants. At this initial stage, a bacterial infection (the current definition of periimplantitis) is not likely, representing only a late complication of marginal bone resorption. In many cases, bone resorption may be active for years without developing periimplantitis, but with increasing time and loss of bony support, a secondary bacterial superinfection is gradually becoming a likely scenario; hence, periimplantitis may represent a complication to already ongoing bone resorption of an aseptic nature.

When bacterial colonization has finally set in, we may have a dual source of recruitment of bone resorbing cells, one of an aseptic and the other of a septic origin.[6,43,44] In other words, infection is not likely to be the initial trigger of bone resorption, but biomaterials may activate innate and/or adaptive immunity in a similar way to that of bacterial lipopolysaccharides. In fact, it has been suggested that the gradual development of periimplant bone loss may be based entirely on a foreign body reaction.[5,6]

Soft Tissues and Foreign Body Equilibrium

The soft tissue seal around dental implants is fundamental for the long-term success of osseointegrated dental implants. Mucosa, like skin, represents the first barrier and first line of defense against external aggressions against the human body. Langerhans cells are DCs that can be found in skin and mucosa (including the oral one)[45] and are known to represent the most peripheral outpost of the immune system.[46] Because these cells are antigen presenting and of mononuclear origin, like macrophages, a role in the foreign body reaction could be expected. Macrophages and their fusion into foreign body giant cells, as stated, are considered a hallmark of the foreign body reaction, although it is believed that a great part of the ensuing reactions to biomaterials are controlled by these cells[6] through inflammatory mediators and interactions with lymphocytes, fibroblasts (in soft tissues), and osteoblasts/osteoclasts (in hard tissues).

Myeloid DCs are equally considered important bridges between the innate and adaptive immune systems, playing a role in many inflammatory diseases through processes still not entirely understood,[47] eliciting a potential role for the foreign body reaction, a similar inflammatory process with immunologic characteristics. It has been suggested further that biomaterials are agonists for DCs maturation and influence the phenotype developed, with repercussions for the immune response guiding the foreign body reaction.[48]

An in vitro study has found that Langerhans cells in the oral mucosa are more effective in stimulating T cells than their skin counterparts.[49] In another in vitro study, the same authors concluded that this might be owing to a suppressive factor in the skin environment, although such a factor has not been identified.[50] Clarification is needed for such relationship between immune cells on the oral mucosa and biomaterials, and how this can affect the success of the treatment with implantable devices.

Psoriasis is an autoimmune disease and the differences in behavior of DCs in skin lesions of patients with such ailment have been addressed. It has been reported that there is an inflammatory dermal DC phenotype $CD11c^{+}CD1c^{-}$ in psoriatic skin lesion areas, when compared with a resident cutaneous DC phenotype is $CD11c^{+}CD1^{+}$; the inflammatory DCs express a higher amount of inflammatory mediators.[47]

It would be of interest to investigate whether different DC phenotypes exist in the soft tissue displaying periimplant disease in the oral mucosa and whether these patients have actually been diagnosed previously with any immunologic dyscrasia. Having said this, there is a lack of evidence that marginal bone resorption must be preceded by mucositis, as suggested by some clinical scientists.

Keratinocytes of the basal layer are responsible for the continued supply of differentiated cells for reepithelization.[51] It remains to be understood whether, after implant insertion of a transmucosal implant, the dynamic process of the soft tissue to reepithelize is maintained, or whether this ability is negatively affected under inflammatory conditions, such as those caused by the surgical procedure to place the implant or resulting from the mere long-term tissue contact with the biomaterial, representing an altered foreign body equilibrium.

Furthermore, inflammatory DC phenotypes produce inflammatory mediators, including tumor necrosis factor–related, apoptosis-inducing ligand, which could have a direct effect on keratinocytes and/or other skin cell types to promote disease pathogenesis.[47]

Another important aspect in the periimplant soft tissue equation is the basement membrane. In the skin, the basement membrane firmly attaches the epidermis to the dermis and in the mucosa it connects the epithelium to the underlying connective tissue. Problems at the basement membrane form the basis of pathologies like epidermolysis bullosa, which can affect individuals in a hereditary fashion, both at the mucosal and skin level, causing clinical fragility and blistering of these structures.[52] An in vitro study suggests that production of the protein components (different kinds of collagen, integrins, laminin, etc) depends on keratinocytes and fibroblasts.[52]

When considering implant biomaterials, periimplant soft tissue loss or unfavorable transformation could be related hypothetically to changes at the basement membrane that can result from alterations in fibroblasts, keratinocytes, collagen, laminin, integrin, and other relevant factors, especially those with inflammatory and/or immunologic roles, that could ultimately influence the foreign body reaction process guiding the implant–tissue integration. Hence, the soft tissue integration is also likely to depend on a foreign body type of reaction and is intimately related to the material surface characteristics and composition. Integrity can be threatened equally by potentially pathologic conditions independent of bacterial colonization.

OSSEOINTEGRATION DYNAMICS

Following this explanation, osseointegration seems to depend not on a single pathway, but on a build-up system, whereas marginal bone loss depends on a breakdown system of reactions.[6] These systems characterize the dynamic nature of osseointegration; we now term these systems of reactions osseointegration dynamics (**Fig. 1**), which ensures that all parts considered are valued and taken into account. Osseointegration dynamics brings other challenges. It emphasizes the nonperennial nature of oral implants osseointegration, meaning that implants have to be followed, with clinicians paying special attention to overload situations or initial inflammatory conditions that need prompt intervention, because these tend to be asymptomatic, if displaying initial bone resorption.

Osseointegration dynamics relates to the in vivo lifetime of the implant and is intimately related to long-term clinical success. It also leaves open doors to the development of different strategies to deal with periimplant pathology, and it motivates the development of better, more predictable, faster healing dental implants, which can only be achieved with a thorough understanding of osseointegration biology.

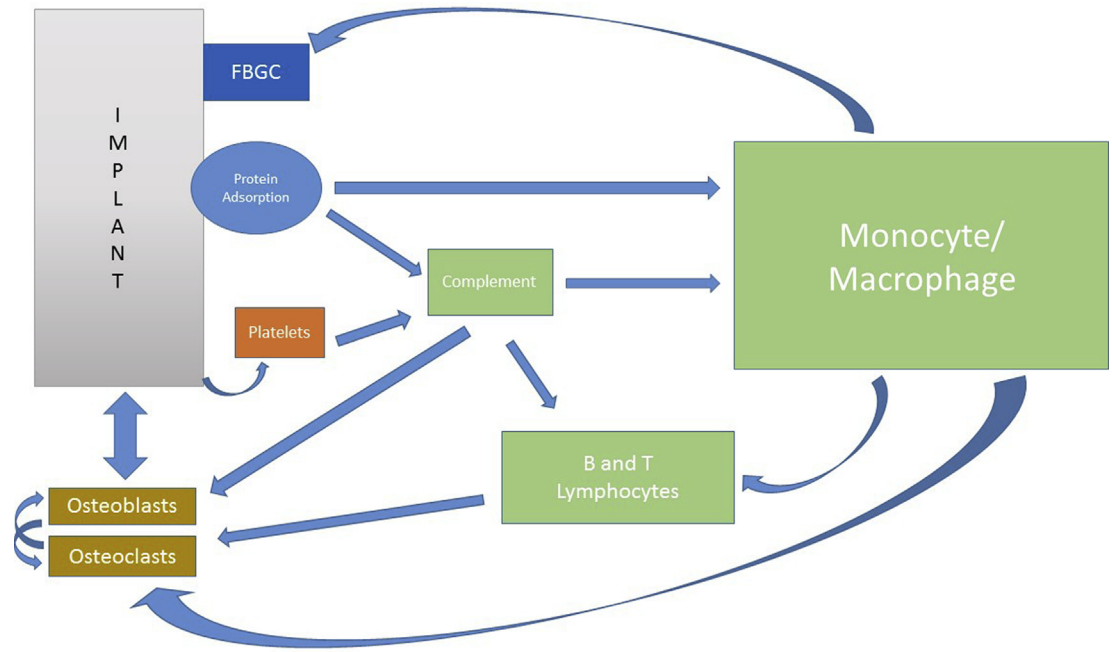

Fig. 1. Hypothetical model for osseointegration dynamics. FBGC, foreign body giant cells.

SUMMARY

Understanding the biology behind implant dentistry is of tremendous importance, because it opens the door to what should guide the development of solutions in the field: putting aside heuristic methods and replace them by methods that produce solutions to achieve a specific biological goal. It is obvious that trial and error will always be a part of science, as it, in its very essence, proposes to explore the unknown. But understanding biology is as important for scientists aiming at developing ever more predictable dental implant solutions as it is for clinicians upon deciding what is best for their patients, whether regarding a technique, a material or a whole treatment protocol.

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