Is Osseointegration a Foreign Body Reaction?

John E. Davies, BSc, BDS, PhD, DSc, FBSE

It is now an almost legendary story that, while undertaking animal experiments to study blood flow in bone using titanium chambers,\(^1\) Per-Ingvar Brånemark was alert to the finding that the chambers were difficult to remove at the end of the experiment—and thus the term “osseointegration” entered the lexicon of implant dentistry.

Since then, there have been many definitions of osseointegration. The variety of these definitions attests to the difficulty in identifying a single characterization of the multiple biologic processes that result in bony anchorage sufficient for an implant to withstand functional loading. Brånemark himself (citing a Skalak and Brånemark workshop report in 1995)\(^2\) provided one reason for the multiple definitions that have been published over the last half-century: osseointegration can be seen from the perspective of the clinician, biologist, chemist, materials engineer, and physicist, all of whom will regard the phenomenon from different points of view. However, seen from only one point of view, each definition will fail to capture the complexity of the phenomenon under discussion.

Such differences in perspective continue today, with the most recent definition of osseointegration as “a foreign body reaction where interfascial bone is formed as a defense reaction to shield off the implant from the tissues.”\(^3\) I am troubled by this definition not only for the paucity of supporting scientific evidence, but also because it has become a popular subject of conferences and similarly promulgated in reports that seek to repeat the dogma without attempting to question the veracity of its claims.

Notwithstanding the constitutive contradiction within the definition (bone is itself a living tissue), an implant is a foreign body and, upon implantation, there is indubitably a biologic reaction to this foreign body. But this begs the question: Does this represent a “foreign body reaction” (FBR)?

Fortunately, there is extensive literature describing the FBR,\(^4,5\) which is also known as a foreign body response and histologically as a foreign body granuloma.\(^6\) The FBR against biomaterials has been characterized as an interfascial phenomenon\(^6\) comprising five stages: (1) protein adsorption; (2) acute inflammation; (3) chronic inflammation; (4) foreign body giant (FBG) cell formation; and (5) fibrosis or fibrous capsule formation.\(^7\) Of course, acute inflammation caused by surgical damage to tissue will trigger the deeply entrenched innate immune system defense response and can lead to resolution of the injury, even in the presence of infection.

The initial effectors of this response are platelets that, upon activation, prime a cascade of cellular signaling. Extravasated neutrophils bind and inactivate bacteria by forming neutrophil extracellular traps (NETs),\(^8\) and rapid injury resolution is facilitated by an early chronic phase of healing marked by the ingress of macrophages and endothelial cells (so-called granulation tissue) with concomitant ingress of perivascular mesenchymal progenitors into the peri-implant wound site.

Macrophages have been commonly associated with a reaction to foreign material, but also play a vital role in cleaning up the tissue damage caused by the surgical insult. The latter creates damage-associated molecular patterns (DAMPs)\(^9\) and constitutive extracellular matrix molecules that are also recognized as foreign to macrophages,\(^10\) which together with pathogen-associated molecular patterns (PAMPs) are collectively known as alarmins.\(^11\) It is now generally held that macrophages express a phenotype along a continuum from M1 (pro-inflammatory, previously FBG, cells) to M2 (regenerative cells),\(^12,13\) and thus a continued presence of macrophages within the peri-implant bone healing compartment could signal a positive healing response rather than chronic inflammation.

In an FBR, acute inflammation transitions to a chronic response characterized by recurrent recruitment of the monocytic precursors to activated phagocytic macrophages, fusion into FBG cells, and sequestration.\(^14\) Indeed, the FBR is commonly considered a form of rejection phenomenon, which is particularly evident in the case of soft tissue particulates, where the mechanical properties of the interface influence the degree of the FBR.\(^15\)

In summary, some of the key characteristics of an FBR are extravasation of monocytes that results in macrophages contacting the foreign material; fusion products of such cells becoming multi-nucleated giant (MNG) cells that occupy the interface with the material; connective tissue encapsulation that, importantly, sequesters both the foreign material and associated MNG cells and is considered the most serious impediment to function\(^15,16\); and interfascial micro-movement that is a determinant of the severity of the FBR. This cell and fibrous tissue arrangement has been reported both histologically and diagrammatically in numerous publications\(^15–17\) and is illustrated in Fig 1a.

EMERGENCE OF THE FBR DEFINITION OF OSSEOINTEGRATION

The FBR definition of osseointegration is encapsulated in five papers\(^3,18–21\) in which the authors argue that when a foreign body is placed in either bone or soft
tissue, an inflammatory reaction inevitably develops. The authors assert that “osseointegration is but a foreign body response to the implant” and a “chronic inflammatory response” that is characterized by the presence of FBG cells that, for the majority of implants, exist in a balanced steady state, for which the authors coined the term “foreign body equilibrium.” This foreign body reaction is invoked as the foundation for the pathology that develops in peri-implantitis, when the foreign body equilibrium is “dis-balanced.”

This theory takes its origin from two papers cited by the authors and published in 1992 by renowned oral pathologist Karl Donath. The first of these papers sought to explain the differences between the pathogenesis of peri-implantitis and periodontitis and stipulates: “Regardless of their design and structural composition, implants are foreign bodies which induce chronic inflammation and a foreign body reaction.” Apart from the obvious point that the author was addressing pathologic conditions rather than healthy peri-implant wound healing, he specifically differentiated between the pathogenic flora found in periodontal and peri-implant tissues. His clinical examples included histologic sections of infected retrieved peri-implant tissue.

In the second paper, Donath et al (1992) specify that “in every case [a foreign body reaction] tends to eliminate the material by rejection, dissolution, resorption, or demarcation.” The majority of the examples provided were of particulate materials—eg, amalgam, carbon, or calcium phosphate ceramic particles—although they also showed macrophages on the surface of titanium particles of a plasma-sprayed screw implant surface. Specifically, Donath et al distinguished between a carbon particle in muscle that was covered by giant cells and loose connective tissue and a carbon block that was immobile during healing in bone that exhibited contact osteogenesis (referred to as “bone conduction”).

The histologic evidence provided by the authors of the FBR definition of osseointegration appears in only two figures from the five papers (Fig 2). Specifically, Albrektsson et al 18 show a low-magnification micrograph of a metallic screw-threaded implant with some non-bony tissue juxtaposed to one thread apex in which no giant cells can be discerned, and Trindade et al 19 provide an image that shows osteoclasts on a bone surface that contains an unidentified biomaterial particle (possibly calcium phosphate) that has broken away from the bulk material on which two darkly stained masses are identified as FBG cells. A chronic inflammatory response is explained by the chronic presence of macrophages that are not evident from the histology presented.
AN ALTERNATIVE INTERPRETATION

In the very initial events of peri-implant wound healing, platelet, neutrophil, macrophage, and MNG cell activation lead to wound resolution, while tissue regeneration is achieved through an influx of perivascular mesenchymal progenitors. In cancellous bone, the marrow-filled interstices provide a readily available source of mesenchymal osteogenic progenitors. In cortical bone, peri-implant regeneration is achieved by the complex process of bony remodeling.

There are many papers reporting MNG cells on the surface of endosseous implants. Examples are found in the exemplary histology from the Robert K. Schenk Laboratory at the University of Bern, two examples of which are reproduced in Fig 3. Saulacic et al\textsuperscript{24} examined endosseous healing with three titanium-based implants. MNG cells were seen on all surfaces to varying degrees, and bone-implant contact (BIC) increased with time.

Similarly, Chappuis et al\textsuperscript{25} reported endosseous healing on yttria-stabilized and alumina-toughed zirconia compared to commercially pure titanium implants. Again, MNG cells were seen on all surfaces, but no inflammatory infiltrate was observed. In all cases discussed in both papers, either bone or MNG cells were in direct contact with the implant surfaces, as illustrated in Fig 1b, and there was no evidence of bony encapsulation, as illustrated in Fig 1c. Indeed, Weingart et al had already shown that fine particles of titanium plasma spray material released from TPS screw implants engulfed by macrophages and transported to local lymph nodes created no inflammatory response or FBR.\textsuperscript{26}

Cross-talk between macrophages and their multinucleate fusion products with osteogenic precursors is instrumental in re-establishing tissue homeostasis, as has been more thoroughly discussed recently.\textsuperscript{27} Miron et al,\textsuperscript{28} noting the stable long-term bone volume around endosseous implants, questioned the FBR hypothesis and proposed that cells identified as proinflammatory foreign body giant cells (an M1 phenotype) could rather be an M2-MNG phenotype and contribute to regeneration. Indeed, M2 macrophages have been shown to signal endothelial and osteogenic cells to stimulate both angiogenesis and osteogenesis\textsuperscript{29} and play a critical role in bone homeostasis.\textsuperscript{30} Interestingly, a prescient 1996 paper by Piattelli et al\textsuperscript{31} hypothesized that the presence of MNG cells may have had a priming effect on the activity of osteoblasts.

In summary, the biologic reaction to a nonparticulate bone implant material cannot be described as an FBR. The latter term has a distinct meaning in both the histopathology and biocompatibility literature. While multinucleate giant cells can be found at the surface of dental implants, they coexist with bone, which is also in direct contact with the same implant. Indeed, MNG cells may play a regenerative role in signaling osteogenesis.

John E. Davies is a professor at the Institute of Biomaterials and Biomedical Engineering (IBBME) of the University of Toronto (Canada), with cross-appointments to the Faculty of Applied Science and Engineering, the Faculty of Dentistry, and the Faculty of Medicine (Department of Surgery). His research focuses on understanding early events in peri-implant healing. Davies trained as an anatomist and oral surgeon in the United Kingdom. He was awarded a DSc by the University of London (England) for his sustained research contributions over a period of 20 years to the field of biomaterials. He has edited 2 books, published over 200 scientific papers and book chapters, and has filed over 70 patents.
REFERENCES


Accuracy of Digital Technologies for the Scanning of Facial, Skeletal, and Intraoral Tissues: A Systematic Review

The accuracy of the virtual images used in digital dentistry is essential to the success of oral rehabilitation. The purpose of this systematic review was therefore to estimate the mean accuracy of digital technologies used to scan facial, skeletal, and intraoral tissues. A search strategy was applied in four databases and in the non-peer-reviewed literature from April 2017 through June 2017 and was updated in July 2017. Studies evaluating the dimensional accuracy of three-dimensional (3D) images acquired via the scanning of hard and soft tissues were included. A total of 2,093 studies were identified by the search strategy, and 183 were initially screened for full-text reading. A total of 34 studies were considered eligible for this review. The scanning of facial tissues showed deviation values ranging between 140 and 1,330 μm, whereas the 3D reconstruction of the jawbone ranged between 106 and 760 μm. The scanning of a dentate arch with intraoral and laboratorial scanners varied from 17 μm to 378 μm. For edentulous arches, the scanners showed a trueness range between 44.1 and 591 μm and between 19.32 and 112 μm for dental implant digital scanning. The current digital technologies are reported to be accurate for specific applications; however, the scanning of edentulous arches still represents a challenge.


—Steven Sadowsky, USA

136 The International Journal of Prosthodontics

© 2019 BY QUINTESSENCE PUBLISHING CO, INC. PRINTING OF THIS DOCUMENT IS RESTRICTED TO PERSONAL USE ONLY. NO PART MAY BE REPRODUCED OR TRANSMITTED IN ANY FORM WITHOUT WRITTEN PERMISSION FROM THE PUBLISHER.