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HOST IMMUNE RESPONSE TO DENTAL BIOMATERIALS: IMPLICATIONS FOR LONG-TERM CLINICAL SUCCESS

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Abstract

The host immune response is a decisive factor governing the long-term success of dental biomaterials and implantable devices, immediately after implantation, the surfaces of the biomaterials interact with host proteins and immune cells, initiating an innate inflammatory cascade, dominated by macrophage activation. Depending on the topography of the material, stiffness and chemical composition, this response can evolve into regenerative osseointegration or chronic foreign body reactions, and fibrous encapsulation and persistent inflammation remain a major factor in implant failure, especially when combined with peri-implant infection, and we have observed that recent advances have shifted the paradigm from inert biocompatibility to biomaterials that train the immune system, this actively directs healing. Strategies such as macrophage polarization to pro-regenerative phenotypes, controlled cytokine delivery, and bioactive ion release have demonstrated improved osteoimmune coupling, and emerging biomimetic scaffolds activate adaptive immune pathways, suggesting broader immunological integration in future implant design. The important thing is to understand the immuno-biomaterial interactions, essential for the development of next-generation dental implants, with increased stability, reduced fibrosis and predictable clinical outcomes, and continuous translational research will support multifunctional platforms that combine immunomodulation, resistance to infections and regenerative capacity.

Keywords: dental biomaterials, host immune response, macrophage polarization, foreign body reaction, osseointegration, immunomodulation

Innate immune recognition of dental biomaterials: initial host response

Immediately after implantation, dental biomaterials are perceived by the host organism as foreign structures, triggering an innate immune reaction that represents the first determinant of long-term clinical integration, and this early phase is not merely a passive inflammatory event but rather a highly orchestrated biological cascade shaped by the physicochemical properties of the implanted surface, and surface topography, stiffness, and surface energy significantly influence protein adsorption and immune cell recruitment, thereby dictating whether the response evolves toward regenerative healing or chronic inflammation. Abaricia et al. highlighted that biomaterial-driven modulation of innate immunity critically depends on micro- and nanoscale surface features, which can actively regulate macrophage behavior and the secretion of inflammatory mediators [1].

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In contemporary implantology, this recognition phase has become central to the emerging concept of implant-mediated immunomodulation. Zhang et al. emphasized that dental implants should no longer be regarded as inert substitutes, but as immune-instructive platforms capable of directing host responses toward enhanced regeneration [2]. The earliest biological interaction is dominated by protein adsorption and provisional matrix formation, particularly fibrin deposition, and this fibrin polymer layer acts as a biological interface that conditions immune cell activation and promotes the foreign body reaction, as demonstrated by Balabiyev et al., who identified fibrin as a key initiator of long-term inflammatory encapsulation [3].

Beyond surface chemistry, the surrounding tissue microenvironment plays an essential role in determining immune outcomes, and Hernandez et al. showed that fibrous capsule formation is not solely material-dependent, but emerges from the dynamic interaction between implant coatings and local stromal conditions, including vascularity and immune cell density [4].

A major clinical complication associated with dysregulated innate immunity is peri-implant infection, in which excessive inflammation compromises osseointegration. Amin Yavari et al. proposed a paradigm shift from antimicrobial strategies targeting bacteria alone toward host-centered approaches that strengthen immune competence and regulate inflammatory balance [5], and this is consistent with the broader development of immune-instructive biomaterials designed to mitigate fibrotic foreign body reactions. Kämmerling et al. discussed how biomaterials can be engineered to minimize chronic macrophage activation and instead promote resolution pathways through immunoregulatory cues [6].

The transition of the macrophage phenotype from pro-inflammatory (M1) to pro-regenerative (M2) is an essential factor for successful tissue integration, and Spiller et al. they demonstrated that sequential cytokine delivery can accelerate this transition and enhance vascularization in bone skeletons, emphasizing the therapeutic importance of immune modulation in the early stages [7], and macrophage responses vary significantly depending on the composition of ceramic scaffolding, with specific biomaterial architectures promoting regenerative patterns of polarization [8], even Vasconcelos et al. further confirmed that fibrinogen-based scaffolding possesses intrinsic immunomodulatory potential, supporting bone regeneration through controlled inflammatory signaling [9].

In addition to cytokines, bioactive ionic dissolution products released from silicate bioceramics have been shown to regulate immune activation and osteogenic coupling. Huang et al. emphasized that ions such as Si and Ca can alter macrophage cytokine profiles and improve osteoimmune synergy [10]. Advanced implant coatings have also enabled localized release of immunomodulatory molecules. Li et al. developed sol–gel layers releasing interleukin-4 to induce M2 polarization directly at the implant interface [11], and surface biofunctionalization of porous titanium implants with immunologically active coatings has emerged as a promising strategy to improve osseointegration [12]. Yang et al. confirmed that integrated micro–nano topographies enhance immune-guided bone healing by optimizing early inflammatory responses [13].

Finally, biomaterials based on natural polymers and nano-hydroxyapatite composites have shown strong immunoregenerative effects, and Chitosan-based scaffolds can induce M2 polarization and promote osteogenic differentiation [14], while sericin/nano-hydroxyapatite hydrogels incorporating graphene oxide further enhance bone repair through combined immunomodulatory and osteoinductive mechanisms [15].

Foreign body reaction and fibrous encapsulation: barrier to long-term clinical success

After the initial phase of innate immune recognition, the host response to dental biomaterials can evolve into a chronic inflammatory cascade known as the foreign body reaction (FBR), and this response represents a central biological barrier to the long-term success

of the implant, especially when inflammatory resolution fails and the tissue environment moves towards fibrotic encapsulation, and we have observed that FBR is characterized by persistent activation of macrophages, the formation of giant multinucleated cells and the remodeling of connective tissue that isolates the biomaterial from the surrounding bone or soft tissue, and this is particularly important to observe because this process is not just a defensive reaction and a complex immunological phenomenon with direct consequences for osseointegration and long-term functional stability.

Recent advances in scaffold engineering have highlighted that biomaterial composition can influence whether immune activation evolves toward regeneration or fibrosis, and Fu et al. demonstrated that sericin/nano-hydroxyapatite hydrogels incorporating graphene oxide stimulate bone regeneration through coordinated immunomodulatory and osteoinductive pathways, suggesting that the FBR is not inevitable but can be redirected when immune cues are properly controlled [15], and when biomaterials fail to induce a regenerative immune phenotype, chronic inflammation may instead dominate, culminating in fibrous tissue encapsulation and reduced implant integration.

A key emerging direction for overcoming fibrotic implant failure is the design of biomimetic scaffolds that modulate both innate and adaptive immunity, and Su et al. described stem cell membrane-coated scaffolds that elicit regenerative immune responses in critical-size bone defects by engaging adaptive immune components alongside innate macrophage pathways and such findings underscore that the FBR is not restricted to macrophages alone, but reflects a broader immune network shaped by antigen presentation and immune cell crosstalk [16].

Dendritic cells play a pivotal role in linking biomaterial-triggered innate responses to adaptive immune activation, and Leifer emphasized that dendritic cell recruitment and maturation at scaffold interfaces can determine whether implanted materials promote tolerance or chronic inflammatory activation, and fibrous encapsulation can be interpreted as an immunologically active outcome rather than a passive scar, representing the host's attempt to biologically quarantine persistent foreign stimuli [17].

This dualistic role of biomaterials as either inflammatory triggers or immune regulators has been conceptualized by Mariani et al., who proposed that modern biomaterials function not only as foreign bodies but also as tuners of immune responses. and their work supports the notion that long-term clinical success depends on achieving immune homeostasis rather than suppressing inflammation indiscriminately [18]. Thus, the fibrotic capsule is increasingly viewed as the endpoint of immune dysregulation rather than a purely mechanical complication.

In regenerative dentistry, scaffold degradation kinetics further complicate immune outcomes. Yang et al. reviewed how immune responses shape the fate of scaffold degradation, emphasizing that inflammatory cell infiltration controls enzymatic remodeling and the balance between constructive tissue regeneration and pathological resorption, and materials that degrade too rapidly may amplify inflammation, whereas those persisting excessively may intensify the chronic foreign body response and fibrosis [19].

From a translational perspective, the future of implant success lies in multifunctional biomaterials that combine structural support with localized immune modulation and drug delivery, and Trucillo highlighted the expanding role of biomaterials as controlled-delivery platforms in clinical applications, underscoring their capacity to actively regulate host responses over time rather than serve as inert replacements, because in dentistry, such approaches could reduce fibrous encapsulation, promote osseointegration, and enhance long-term implant survival [20].

Immunomodulation strategies: directing macrophage polarization toward regeneration

The long-term clinical success of dental implants and regenerative biomaterials increasingly depends on their capacity to modulate host immunity rather than merely avoid

inflammatory activation. In this context, contemporary research has shifted from the paradigm of "biocompatibility as inertness" toward the development of immune-instructive biomaterials designed to actively direct the immune response toward constructive tissue regeneration [6,18]. Among innate immune cells, macrophages represent key regulators of the healing trajectory, as their functional polarization determines whether the implant interface evolves toward chronic inflammation and fibrosis or toward angiogenesis and osteogenesis.

Macrophage activation is commonly described as a spectrum ranging from the classically activated M1 phenotype, associated with pro-inflammatory cytokine release, to the alternatively activated M2 phenotype, which promotes tissue remodeling, vascularization, and resolution of inflammation [7], and surface architecture and physicochemical properties of biomaterials have been shown to strongly influence this polarization balance. For instance, biomaterial surface topography, stiffness, and energy can regulate macrophage adhesion and cytokine secretion, thereby shaping the early immune microenvironment at the implant interface [1].

One of the most effective strategies in regenerative implant design involves controlled delivery of immunomodulatory cytokines, and Spiller et al. demonstrated that sequential cytokine release can promote the M1-to-M2 transition, enhancing vascularization and improving scaffold integration in bone regenerative settings [7], similarly, localized interleukin-4 delivery via sol–gel coatings on TiO_2 nanotubes has been shown to induce M2 polarization, thereby reducing the inflammatory burden while supporting osteogenic healing [11], and we believe that these types of approaches highlight the therapeutic potential of biomaterials as active immune regulators rather than passive frameworks.

In addition to cytokine-based modulation, ceramic and composite scaffolds can intrinsically influence macrophage responses. Graney et al. reported that the composition of ceramic scaffolds affects macrophage behavior in vitro, with certain bioceramic structures promoting regenerative immune phenotypes [8]. Bioactive ion release represents another powerful osteoimmune mechanism: silicate-based bioceramics release ions such as calcium and silicon that modulate macrophage cytokine profiles and enhance bone regeneration through immune–osteogenic coupling [10]. Micro–nano hierarchical surface integration has further been correlated with improved immune-guided osseointegration, suggesting that immunomodulation can be encoded directly in implant architecture [13].

Natural polymer-based scaffolds have also demonstrated strong immunoregenerative properties, and chitosan/agarose/nano-hydroxyapatite constructs induce M2 polarization while promoting osteogenic differentiation, reinforcing the importance of immune-mediated pathways in scaffold-driven regeneration [14], and these materials are particularly relevant because they combine structural support with biological signaling, allowing the scaffold to participate actively in the regulation of inflammation, matrix deposition, and early bone formation, and moreover, the presence of nano-hydroxyapatite provides a biomimetic mineral phase that may improve cellular adhesion and osteogenic commitment, and more advanced hybrid systems, such as sericin/nano-hydroxyapatite hydrogels reinforced with graphene oxide, further enhance osteoinduction through coordinated immunomodulation and bone-formation signaling [15], and together, these findings support the development of multifunctional dental biomaterials that integrate mechanical stability, immune regulation, and regenerative potential within a single therapeutic platform.

Future perspectives include biomimetic strategies integrating adaptive immunity. Stem cell membrane-coated scaffolds have been shown to induce regenerative innate and adaptive immune responses, offering new directions for immunologically optimized bone healing [16], and we have observed that these discoveries together, these discoveries support the concept that successful dental biomaterials must actively orchestrate immune responses, ensuring inflammatory resolution and promoting long-term stable tissue integration [2,5].

Table 1. Key immunomodulatory strategies enhancing regenerative integration of dental biomaterials

Approach	Immune Target Mechanism	Regenerative Outcome	Ref.
Surface micro/nano-topography	Controls early macrophage activation	Improved osseointegration	[1,13]
Cytokine-mediated polarization (IL-4)	Induces M2 pro-healing phenotype	Reduced inflammation, enhanced healing	[7,11]
Bioactive ceramic ion release	Modulates cytokine signaling via Ca/Si ions	Osteoimmune coupling and regeneration	[10]
Natural polymer/NanoHA scaffolds	Promotes M2 polarization + osteogenesis	Bone scaffold integration	[14,15]
Biofunctionalized porous titanium implants	Creates an immune-regenerative interface	Reduced fibrosis, stable anchorage	[12]
Biomimetic immune-adaptive scaffolds	Activates innate + adaptive regenerative immunity	Enhanced defect healing	[16]

In Table 1 we have highlighted condensed immunomodulatory approaches in dental biomaterials, focusing on macrophage polarization control, bioactive ion signaling, and biomimetic scaffolding engineering, and these strategies aim to suppress chronic inflammation and promote regenerative immune environments essential for long-term implant success.

Future directions in dental biomaterials: adaptive immunity, infection control, and clinical translation

The future of dental biomaterials research is increasingly defined by the integration of immunology into implant design, shifting the clinical objective from simple tolerance toward immune-guided regeneration, and while early implantology focused on minimizing inflammation, contemporary evidence suggests that controlled immune activation is essential for achieving stable long-term osseointegration and preventing fibrotic failure [2,6], and thus, next-generation biomaterials are being developed not merely as structural substitutes, but as immune-modulating platforms capable of orchestrating tissue healing.

A major emerging concept is the recognition that host responses extend beyond innate immunity and involve adaptive immune regulation, and dendritic cells, as antigen-presenting mediators, play a pivotal role in determining whether implanted materials promote immune tolerance or chronic inflammatory activation, and Leifer emphasized that dendritic cell engagement within scaffold microenvironments influences downstream adaptive responses, suggesting that immune-compatible biomaterials must account for these regulatory pathways and this adaptive dimension becomes particularly relevant in long-term implantation, where persistent immune stimulation may contribute to chronic peri-implant inflammation [17].

In parallel, implant-related infections remain a major clinical challenge, and traditional approaches have mainly focused on eliminating bacteria, however we have noticed that recent strategies are placing more and more emphasis on strengthening host-directed immune competence, and Amin Yavari et al. proposed that combating implant infections requires shifting from pathogen-centered paradigms to modulating the host inflammatory environment, thereby reducing susceptibility to biofilm-mediated complications and such perspectives align with the broader understanding that immune dysregulation, rather than the mere presence of microbes, often determines implant failure [5].

The advanced biomaterials engineering in our observations provides promising translational solutions, and surface biofunctionalization and porous titanium architectures have

been shown to provide immunomodulatory cues that enhance osseointegration while limiting chronic inflammation [12], and micro-nano integrated surface topographies can enhance immune-mediated bone integration by optimizing early macrophage signaling and regenerative polarization [13]. These findings we observe underscore that implant success increasingly depends on the ability to control immune responses at the interface of biomaterials.

Another key direction we have observed involves biomimetic scaffolds capable of coordinating innate and adaptive immune healing, and these scaffolds covered with stem cell membranes, for example, have demonstrated the ability to trigger regenerative immune cascades in models of critically sized bone defects, suggesting that immune-inspired functionalization could represent a future cornerstone in regenerative dentistry [16]. But the dynamics of scaffolding degradation must also be taken into account, as immune responses strongly influence the decomposition and remodeling of biomaterials. Yang et al. They emphasized that the infiltration of inflammatory cells governs the fate of degradation, determining whether scaffolding supports regeneration or causes pathological resorption and fibrosis [19].

Finally, the clinical translation of active immune biomaterials is closely related to innovations in drug delivery, and Trucillo highlighted the growing role of biomaterials as multifunctional platforms for controlled therapeutic release, allowing localized immunoregulation over extended periods, and such systems can allow the delivery of cytokines, anti-inflammatory agents, or pro-regenerative molecules directly to implant sites, and obtaining minimizing systemic effects and improving tissue integration [20].

In our opinion, future dental biomaterials are likely to evolve towards multifunctional immunoinstructive systems, which integrate resistance to infection, adaptive immune compatibility and regenerative signaling, and the achievement of long-term clinical success will therefore depend on biomaterials designed not only to replace tissue, but also to actively guide host immunity towards stable biological integration [1,18].

Conclusions

Dental biomaterials are no longer understood as passive medical devices but as active modulators of host immunity. The early innate immune response, driven by surface characteristics and protein adsorption, initiates a cascade that can promote either regeneration or chronic inflammation, and when immune resolution fails, foreign body reaction and fibrous encapsulation may compromise osseointegration and long-term clinical performance, and therefore deciphering immune–biomaterial interactions has become essential for improving implant success and reducing inflammatory complications.

Future progress in dental biomaterials will rely on the design of immune-instructive platforms that orchestrate balanced innate and adaptive responses, and strategies such as macrophage polarization control, cytokine delivery, bioactive ion release, and biomimetic functionalization offer promising pathways toward enhanced healing and reduced fibrosis, and host-centered approaches to infection prevention highlight the importance of immune regulation beyond antimicrobial activity alone, and integrating osteoimmunology, scaffold degradation dynamics, and localized drug delivery will support the development of next-generation implants with improved long-term stability, clinical predictability, and regenerative outcomes.

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