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REVIEW

Osteoimmune Regulation in Dental Implant Osseointegration: From Foreign Body Response to Therapeutic Immunomodulation—A Narrative Review

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Background: The long-term success of dental implants depends on osseointegration, traditionally viewed as a biomechanical process. Recent osteoimmunology research reveals it as an immune-mediated phenomenon, where successful integration results from a redirected foreign body reaction termed Foreign Body Equilibrium (FBE).

Objective: This review aims to redefine osseointegration through the lens of osteoimmunology, emphasizing macrophage polarization (M1-to-M2 switch) as the pivotal determinant of implant fate, and to evaluate strategies for immunomodulatory implant design.

Methods: A comprehensive literature search was conducted using databases including PubMed, Web of Science, and Scopus. We selected and synthesized pivotal studies focusing on the cellular and molecular mechanisms of osseointegration, specifically targeting macrophage-T cell crosstalk and the RANKL-OPG axis. The review critically analyzes modulatory factors (surface topography, wettability, patient-specific conditions) and evaluates emerging therapeutic strategies such as bioactive coatings and extracellular vesicle functionalization.

Conclusion: Osseointegration is an active osteoimmune process. Harnessing immunomodulation—particularly macrophage polarization—can transform implants from passive devices to therapeutic platforms, improving outcomes in diverse clinical scenarios.

Keywords: osseointegration, foreign-body reaction, immunomodulation, dental implants, macrophage activation, bone-immune system

Introduction

Dental implant therapy has emerged as the gold standard for replacing missing teeth, with success rates exceeding 95% in healthy individuals. The biological foundation of this success lies in osseointegration, a process first described by Brånemark as the direct structural and functional connection between living bone and the load-bearing implant surface.[1] However, this classical definition, while clinically relevant, fails to capture the complex immunological processes that govern implant integration.[2]

Recent advances in osteoimmunology have fundamentally transformed our understanding of bone-implant interactions. Rather than viewing osseointegration as a purely mechanical phenomenon, contemporary research recognizes it as a dynamic, immune-mediated process.[3] Any biomaterial implanted within the body inevitably triggers a foreign body reaction (FBR), a universal immune response to non-degradable materials. Traditionally, the FBR progresses through predictable stages: protein adsorption, acute inflammation, chronic inflammation, foreign body giant cell formation, and ultimately fibrous encapsulation—signifying implant failure.[4] However, before these chronic stages, the initial wound

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healing phase is critical, where the immune system must efficiently clear debris and resolve acute inflammation to pave the way for tissue repair.

The paradigm shift introduced by osteoimmunology suggests that successful osseointegration represents a unique redirection of the FBR, where the immune system constructs a "biological capsule" of bone tissue rather than a fibrous barrier. This state, termed Foreign Body Equilibrium (FBE), represents a continuously maintained balance between immune surveillance and tissue integration.[5] Understanding this osteoimmune dialogue is crucial for developing next-generation implant therapies that actively modulate host responses to achieve predictable, long-term success[6] (Figure 1).

While recent reviews, such as Kondo et al (2024), have elegantly outlined the innate immune regulations in osseointegration, there remains a need to systematically integrate these mechanisms with advanced therapeutic immunomodulation strategies. Distinct from previous works, this review specifically focuses on the "Foreign Body Equilibrium" concept and critically evaluates how emerging biomaterial technologies—from extracellular vesicles to cell-membrane camouflage—can actively engineer this immune balance for clinical success.

The Foreign Body Equilibrium: Redefining Osseointegration

From Biomechanical Fixation to Immunological Integration

The traditional biocompatibility paradigm emphasizes material inertness and the absence of adverse reactions. However, contemporary osteoimmunology reveals that successful osseointegration requires active immune participation rather than immune avoidance.[7] Upon implantation, the implant surface is immediately coated with host proteins through a process of competitive adsorption, forming a "provisional matrix" that serves as the primary interface for cellular recognition.[8]

This protein corona is not merely a passive film but constitutes the "first language" of host-implant communication. The composition, conformation, and density of adsorbed proteins directly influence subsequent cellular responses, particularly macrophage adhesion and activation.[5] Surface hydrophobicity can induce protein unfolding, exposing cryptic epitopes that may be recognized as damage-associated molecular patterns (DAMPs), thereby initiating robust immune responses.[9]

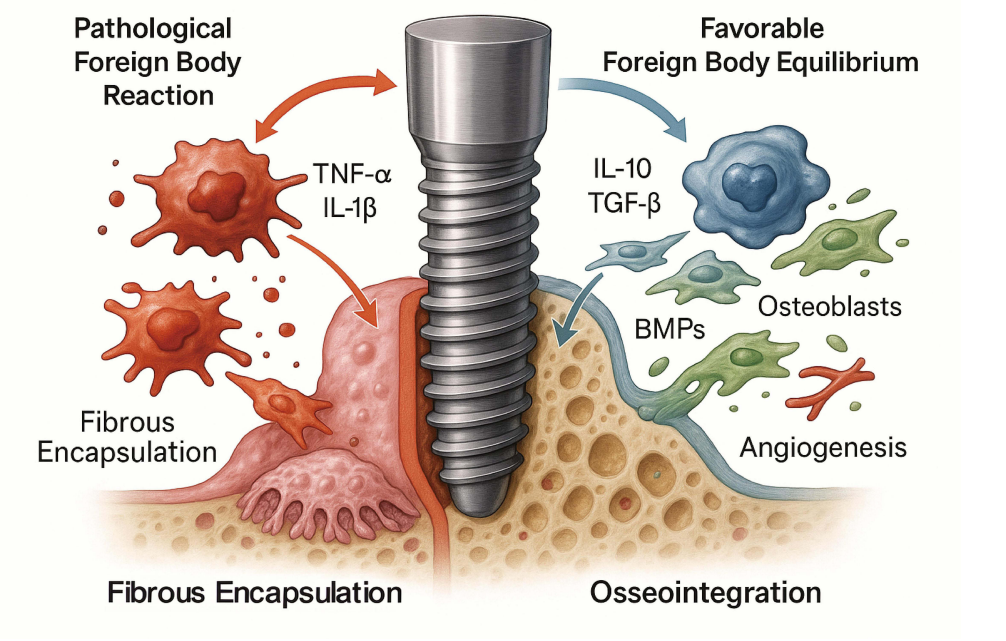

Figure 1 The Dichotomy of the Foreign Body Reaction at the Dental Implant Interface. The fate of a dental implant is determined by the host's osteoimmune response. (Left Panel) A pathological foreign body reaction is characterized by the dominance of pro-inflammatory M1 macrophages, which release cytokines such as TNF-α and IL-1β. This sustained inflammation leads to fibrous encapsulation, preventing direct bone-to-implant contact and resulting in clinical failure. (Right Panel) Successful osseointegration is achieved through a state of "Foreign Body Equilibrium". This favorable outcome is orchestrated by a timely shift to anti-inflammatory M2 macrophages, which secrete cytokines like IL-10 and TGF-β, and growth factors such as BMPs. These factors promote angiogenesis and stimulate osteoblasts to form new bone directly on the implant surface, leading to stable integration.

The Inflammatory Cascade: A Double-Edged Sword

Surgical implant placement inevitably triggers acute sterile inflammation, characterized by the rapid recruitment of neutrophils followed by monocyte infiltration and macrophage differentiation. This initial inflammatory response serves essential functions in debris clearance and wound healing initiation. For biocompatible materials, this acute phase should be transient, resolving within approximately two weeks and transitioning to a pro-reparative environment.[10]

However, persistent inflammation represents a pathological deviation that leads to chronic tissue destruction. Factors such as bacterial contamination, excessive surgical trauma, or continuous particle release can sustain inflammatory responses, ultimately resulting in fibrous encapsulation and osseointegration failure.[11] The immune system thus functions as a "biological switch"—controlled acute inflammation promotes bone regeneration, while uncontrolled chronic inflammation destroys it.

Cellular Orchestrators of the Osteoimmune Response

Macrophage Polarization: The Master Regulatory Switch

Macrophages represent the central coordinators of the FBR and osseointegration process, exhibiting remarkable phenotypic plasticity in response to environmental cues.[12] The classical M1/M2 polarization paradigm, while simplified, provides a useful framework for understanding macrophage functions in implant integration.

M1 Macrophages: Essential Clearance but Potential Destruction

Classically activated M1 macrophages dominate the early post-implantation period, secreting high levels of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).[13,14] While essential for pathogen clearance and debris removal, sustained M1 activation promotes chronic inflammation and bone resorption through enhanced osteoclast activity via the RANKL-RANK signaling pathway.[15]

Titanium wear particles represent potent M1 inducers, activating the NLRP3 inflammasome and triggering the release of mature IL-1β, which creates a destructive positive feedback loop leading to aseptic loosening.[16] This creates a clinical paradox regarding surface topography: while surface roughening (eg, via SLA) is intended to increase the surface area for osseointegration, it may inadvertently compromise the material's wear resistance. Under mechanical loading, increased roughness can accelerate the liberation of titanium ions and particles. These debris are phagocytosed by macrophages, triggering NLRP3 inflammasome activation and sustaining a chronic inflammatory state that counteracts the initial benefits of the roughened surface.

M2 Macrophages: Architects of Tissue Regeneration

Alternatively activated M2 macrophages emerge as inflammation resolves, secreting anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β).[17] These cells actively promote angiogenesis, extracellular matrix remodeling, and osteoblast differentiation through the release of growth factors including vascular endothelial growth factor (VEGF) and bone morphogenetic proteins.[18]

The transition from M1 to M2 phenotype represents the most critical checkpoint determining osseointegration success or failure. This phenotypic switch is regulated by multiple signals, including apoptotic neutrophil clearance, T lymphocyte-derived cytokines, and implant surface characteristics. Delayed or impaired M1-to-M2 transition results in persistent inflammation and ultimate implant failure (Figure 2).

T Lymphocytes: Adaptive Immune Modulators

While the FBR has traditionally been considered a primarily innate immune phenomenon, mounting evidence reveals significant adaptive immune involvement.[19] Dendritic cells can process implant-derived "antigens"—including metal ions, wear debris, or adsorbed bacterial products—and present them to T cells, initiating specific adaptive responses.[3]

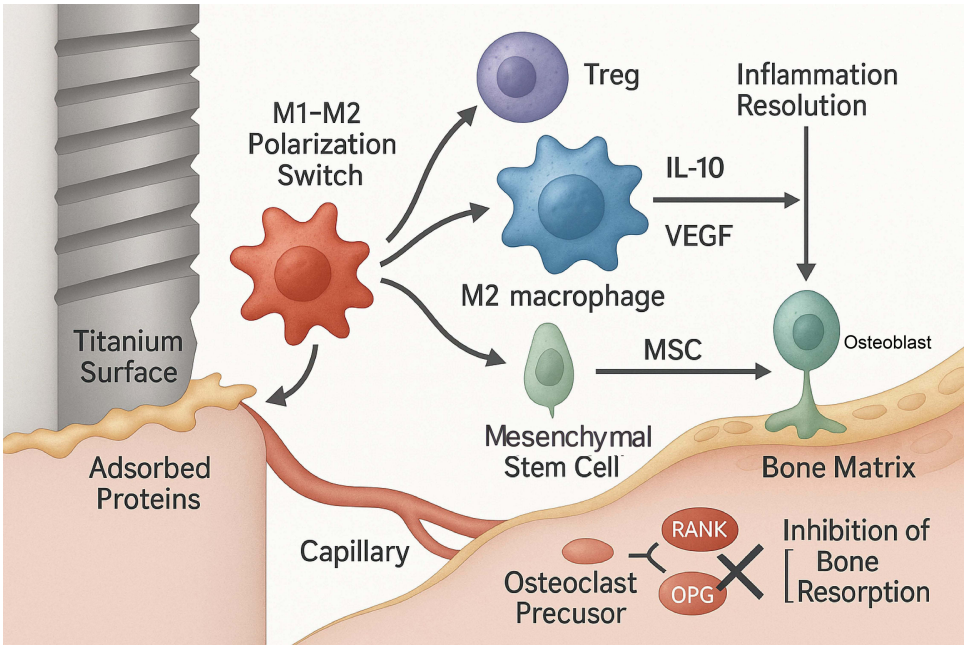

Figure 2 Cellular and Molecular Network Orchestrating Successful Osseointegration. This diagram illustrates the detailed mechanisms driving a favorable osteoimmune response. Upon implantation, host proteins adsorb to the titanium surface. The critical event is the M1-to-M2 macrophage polarization switch, which is promoted by regulatory T cells (Tregs). The resulting M2 macrophages are central coordinators, releasing IL-10 to resolve inflammation and VEGF to promote angiogenesis. They also stimulate mesenchymal stem cells (MSCs) to differentiate into bone-forming osteoblasts. Concurrently, the RANK-RANKL-OPG signaling axis is modulated to favor bone formation, with OPG inhibiting RANK on osteoclast precursors, thus preventing bone resorption.

Th Cell Subsets and Bone Homeostasis

The balance between different T helper (Th) cell subsets critically influences bone metabolism:

- Th1/Th2 Axis: Th1 cells secrete interferon-γ (IFN-γ), promoting M1 macrophage activation and pro-inflammatory responses. Conversely, Th2 cells produce IL-4 and IL-13, driving M2 polarization and tissue repair.[20]
- Th17/Treg Axis: Th17 cells represent a potent pro-inflammatory subset whose signature cytokine, IL-17, strongly promotes osteoclast formation and bone resorption. These cells serve as key drivers of pathological bone loss in periodontitis and peri-implantitis.[21]

Regulatory T Cells: Guardians of Immune Homeostasis

Regulatory T cells (Tregs) function as immune "peacekeepers," suppressing excessive inflammatory responses to maintain tolerance.[22] Tregs protect bone tissue through multiple mechanisms: direct inhibition of osteoclast formation, secretion of anti-inflammatory cytokines, and induction of macrophage M2 polarization. Importantly, Tregs can release extracellular vesicles expressing CD73, which converts ATP to adenosine, acting on macrophage A2A receptors to promote M2 polarization.[23]

In pathological states such as peri-implantitis, an imbalance in the Treg/Th17 ratio, characterized by relative Treg depletion, drives immune dysregulation and progressive bone destruction.[24]

Key Signaling Networks in Osteoimmunology

Two critical signaling pathways govern the osteoimmune dialogue:

The RANK-RANKL-OPG Axis

This pathway represents the master regulator of bone resorption. RANKL (Receptor Activator of Nuclear Factor κB Ligand), expressed by osteoblasts, osteocytes, and activated T cells, binds to RANK on osteoclast precursors, triggering their differentiation into mature bone-resorbing cells.[25] Osteoprotegerin (OPG) acts as a decoy receptor, preventing RANKL-RANK interactions and inhibiting osteoclastogenesis. Pro-inflammatory cytokines disrupt this balance by

upregulating RANKL expression, leading to pathological bone loss. Recent studies indicate that hydrophilic surfaces can downregulate RANKL expression in T cells, thereby shifting the balance towards osteogenesis.

NLRP3 Inflammasome Activation

The NLRP3 inflammasome functions as a danger sensor within macrophages, responding to biomaterial particles and other stress signals.[26] Upon activation, it processes pro-IL-1β into its mature, highly potent form, creating inflammatory amplification loops that drive aseptic loosening and bone destruction. Consequently, modern immunomodulatory coatings, such as those incorporating miRNAs, specifically target the inhibition of NLRP3 assembly to prevent this inflammatory amplification.

Factors Modulating the Osteoimmune Response

Implant Surface Characteristics

The implant surface serves as the primary interface dictating subsequent immune responses through its physical topography and chemical composition.[27] The immunomodulatory efficacy of these modifications is typically characterized using a combination of gene expression analysis (RT-qPCR for cytokine markers), protein secretion profiling (ELISA or Western blot for IL-10/TNF-α ratios), and detailed flow cytometry to assess macrophage M1/M2 surface marker shifts (eg, CD86 vs CD206).

Surface Topography and Immune Modulation

Micro- and nano-scale surface features profoundly influence cellular behavior. Moderately rough surfaces created by sandblasting and acid-etching (SLA) significantly increase surface area for cell attachment while promoting favorable protein adsorption profiles.[28] Specific nanotopographies can reduce macrophage activation and guide M2 polarization, with approximately 30 nm diameter titanium nanotube arrays preferentially inducing M2 phenotypes compared to larger structures.[29]

Surface Chemistry and Wettability

Hydrophilic surfaces promote more favorable protein adsorption and accelerate early bone healing compared to hydrophobic counterparts.[30] SLActive surfaces demonstrate reduced pro-inflammatory cytokine expression by adherent macrophages while enhancing anti-inflammatory factor production. The introduction of specific chemical functional groups (eg, $-NH_2$, -COOH, -OH) can significantly modulate immune cell interactions, with negatively charged surfaces potentially promoting Treg formation.[31]

Tribocorrosion and Mechanical Modulators

Beyond topography and chemistry, the tribocorrosion behavior of the implant surface is a potent immunomodulator. The synergistic effect of mechanical wear and electrochemical corrosion releases metal ions that act as haptens, activating T cells and perpetuating inflammation. Surface treatments that enhance hardness and corrosion resistance, such as nitriding or diamond-like carbon (DLC) coatings, have been shown to mitigate this immune reactivity, preserving the integrity of the osseointegration interface.

Bioactive Ion Integration

The incorporation of bioactive ions into surface coatings represents an emerging immunomodulatory strategy. Strontium (Sr^{2+}) exhibits "dual-action" capabilities, simultaneously promoting osteoblast proliferation while inhibiting osteoclast activity.[32] Importantly, strontium induces macrophage M2 polarization and reduces pro-inflammatory cytokine expression.[33] Similarly, zinc (Zn^{2+}) modifications demonstrate both osteogenic and antibacterial properties while promoting anti-inflammatory responses.

Surgical Technique Considerations

Surgical trauma directly influences the magnitude and duration of inflammatory responses.[34] Minimally invasive techniques, including flapless implant placement, generate less tissue damage and consequently milder inflammatory responses compared to conventional approaches. Clinical studies demonstrate reduced matrix metalloproteinase-8 (MMP-8) levels and decreased marginal bone loss in flapless procedures.[35]

However, the relationship between surgical trauma and healing is complex. Excessive minimization of immune activation may impair the recruitment of regenerative cells necessary for optimal bone formation.[36] The optimal approach balances trauma reduction with sufficient immune stimulation to drive regenerative processes.[37]

Host-Specific Factors

Patient-specific characteristics significantly influence osseointegration outcomes through their effects on systemic and local immune environments.[38]

Age-Related Immunosenescence

Aging is associated with immunosenescence and chronic low-grade inflammation ("inflammaging"), which can compromise osseointegration.[39] Age-related changes in mesenchymal stem cell (MSC) differentiation bias toward adipogenesis rather than osteogenesis, while immune dysfunction may impair proper inflammatory resolution.[40]

Systemic Disease Impact

Diabetes mellitus represents a significant risk factor due to its association with chronic systemic inflammation and M1 macrophage bias.[41] Hyperglycemia promotes sustained pro-inflammatory environments that impair normal bone remodeling and may interfere with MSC osteogenic differentiation. Studies in diabetic models reveal NLRP3 inflammasome hyperactivation and M1/M2 imbalances around implants.[42]

Oral Microbiome Influence

The oral microbiome directly impacts peri-implant immune homeostasis. Microbial dysbiosis, characterized by pathogenic bacterial overgrowth, provides continuous immune stimulation leading to chronic inflammation. This persistent inflammatory state gradually erodes the bone-implant interface, ultimately resulting in peri-implantitis and implant failure.[43]

Therapeutic Immunomodulation Strategies

To actively promote a pro-reparative environment, various therapeutic interventions—ranging from pharmacological agents to advanced biomaterial coatings—have been developed (Table 1).

Pharmacological Interventions

PDRN (Polydeoxyribonucleotide) Therapy

PDRN activates adenosine A2A receptors, inducing macrophage M2 polarization while increasing IL-10 and VEGF production.[45] Clinical studies demonstrate PDRN's ability to suppress RANKL-mediated osteoclast differentiation and promote tissue regeneration in inflammatory environments.[46] As a small molecule therapeutic, PDRN shows high clinical translation potential.

Table 1 Summary of Recent Studies on Immunomodulatory Approaches for Dental Implants

Strategy	Target Mechanism	Key Experimental Outcome (in vitro/in vivo)	Representative Study
Cytokine Delivery	IL-4 immobilized coating	Significant increase in Arg-1 expression (M2 marker) and reduced fibrous capsule thickness in vivo.	[13]
Surface Topography	Nanotube arrays (30–100nm)	30nm tubes promoted M2 macrophage polarization and increased IL-10 secretion compared to smooth Ti.	[29]
Ion Incorporation	Strontium (Sr^{2+}) doping	Downregulation of TNF-α and IL-6; enhancement of osteogenic differentiation in MSCs via Wnt pathway.	[33]
Exosomes/EVs	M2-derived EVs	Suppression of NLRP3 inflammasome activation; restoration of osseointegration in diabetic rat models.	[42]
Biomimetic Coating	CD47 functionalization	"Don't eat me" signal reduced macrophage attachment and foreign body giant cell formation.	[44]

Cytokine-Based Modulation

Direct delivery of anti-inflammatory cytokines such as IL-4 and IL-10 represents a targeted immunomodulatory approach.[47] IL-4-loaded coatings effectively drive macrophage M2 polarization while suppressing inflammatory responses, leading to enhanced bone formation in animal models.[13]

Advanced Biomaterial Strategies

Extracellular Vesicle Functionalization

(Figure 3) M2 macrophage-derived extracellular vesicles (M2-EVs) contain immunomodulatory microRNAs, including miR-23a-3p, which suppress NLRP3 inflammasome activation and reduce IL-1β levels. Polydopamine-mediated M2-EV coating significantly improves osseointegration quality in diabetic models by reversing M1 bias and restoring immune balance.[42]

Dual-Functional Ion-Peptide Coatings

Biomimetic mussel adhesion-mediated coatings enable simultaneous delivery of immunomodulatory Zn^{2+} ions and osteoinductive BMP-2 peptides.[48] This dual-functional approach achieves synergistic effects: Zn^{2+} promotes M2 macrophage recruitment (~92% increase) while BMP-2 directly stimulates osteoblast differentiation, resulting in superior bone-implant contact rates (82.1% vs 45.1% for uncoated controls).[49]

Biomimetic Cell Membrane Camouflage

Cell membrane coating technology represents a revolutionary "top-down" approach, where implant surfaces are cloaked with natural cell membranes (eg, red blood cell membranes) carrying "self-recognition" proteins such as CD47. This strategy effectively evades immune recognition, significantly reducing FBR intensity while maintaining biocompatibility.[44]

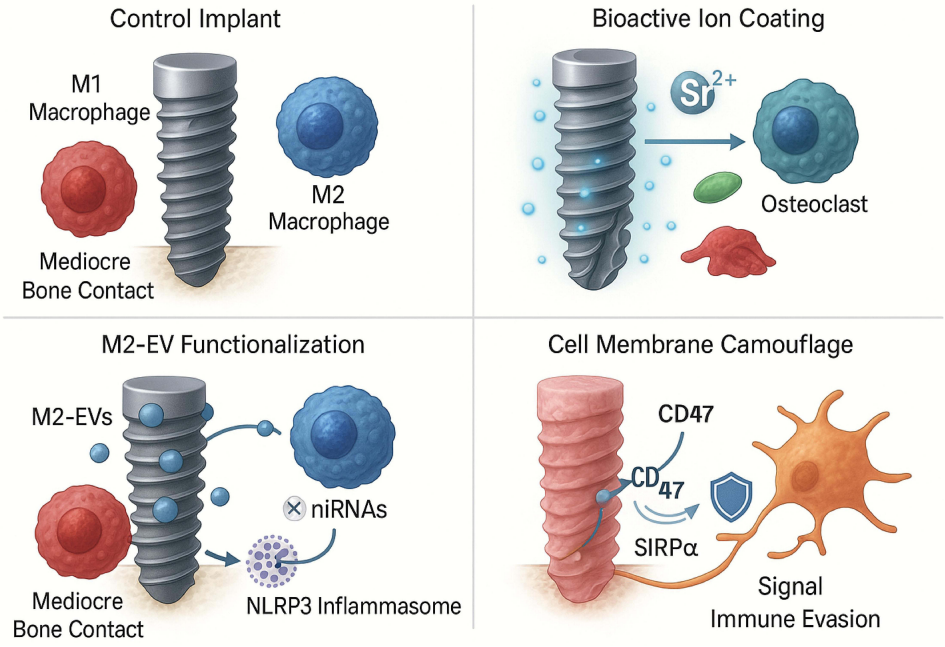

Figure 3 Advanced Immunomodulatory Strategies to Enhance Osseointegration. This figure compares a control implant with several advanced surface modification strategies designed to modulate the host immune response. (Top Left) A control implant elicits a mixed M1/M2 macrophage response, leading to mediocre bone contact. (Top Right) Bioactive ion coatings, such as those releasing Strontium (Sr^{2+}), can promote M2 macrophage polarization while inhibiting osteoclast activity. (Bottom Left) M2-EV functionalization involves coating the implant with M2 macrophage-derived extracellular vesicles (M2-EVs). These EVs deliver microRNAs (miRNAs) that can suppress the NLRP3 inflammasome within M1 macrophages, re-educating them toward a pro-reparative phenotype. (Bottom Right) Cell membrane camouflage uses natural cell membranes displaying "don't-eat-me" signals like CD47, which interacts with the SIRPα receptor on macrophages to evade immune recognition and reduce the foreign body reaction.

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Smart Responsive Systems

The next frontier involves environment-responsive "smart" implants capable of dynamic immunomodulation.[50] pH-sensitive hydrogel coatings can detect infection-induced acidification and respond by releasing antimicrobials and anti-inflammatory agents on demand.[51] Such systems represent the evolution from passive implants to active therapeutic devices capable of real-time adaptation to changing biological conditions.

Clinical Translation Challenges and Future Perspectives

Translational Barriers

While preclinical data are encouraging, the translation to clinical practice faces distinct hurdles. First, regulatory complexity is a major barrier; implants with bioactive coatings or drug-eluting properties are often classified as combination products, requiring stringent safety data regarding release kinetics and systemic toxicity.[52] Second, manufacturing reproducibility remains challenging. Scaling up nano-topographical modifications or delicate biological coatings (eg, cell membranes) without batch-to-batch variability is difficult and costly.[53] Finally, the discrepancy between healthy animal models and compromised human patients (eg, smokers, diabetics) often leads to inconsistent clinical outcomes.[54]

Toward Personalized Immunomodulation

The "one-size-fits-all" approach is becoming obsolete. Future strategies must integrate immune profiling, where patients are stratified based on their cytokine baselines or genetic susceptibility to inflammation (eg, IL-1 polymorphisms).[55] Emerging Artificial Intelligence (AI) and machine learning models could predict implant success by analyzing these complex immune signatures.[56] Furthermore, 3D-printing technologies now allow for the fabrication of patient-specific implants with customized porous structures designed to modulate the local immune niche according to the individual's bone density and inflammatory status.[57]

Advanced Preclinical Models

The development of patient-derived "organ-on-chip" and three-dimensional bioprinted tissue models will enable more predictive testing of implant responses before surgery.[58] These platforms may bridge the translational gap between animal models and human clinical outcomes.

Conclusions

Osseointegration is fundamentally an immune-modulated process governed by the Foreign Body Equilibrium. This review highlights that the long-term success of dental implants relies not on immune evasion, but on the precise manipulation of the host response—specifically, the timely polarization of macrophages from the M1 to the M2 phenotype. While surface modifications and bioactive coatings show immense potential in preclinical models, overcoming regulatory and manufacturing hurdles remains essential. Ultimately, the integration of personalized immune profiling with smart, responsive biomaterials represents the future of implant dentistry, transforming implants from passive devices into active therapeutic tools for tissue regeneration.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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