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Review Article

The Influence of Innate Immunity on Osseointegration: An Osteoimmunological Perspective

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Abstract

Osseointegration has traditionally been defined as a structural phenomenon dependent on the "bio-inert" properties of titanium. However, contemporary "osteoimmunology" redefines implant success as an immune-modulated outcome of the Foreign Body Reaction (FBR). This review examines the aseptic biological mechanisms where the innate immune system determines the fate of dental implants. It focuses on the sequential activation of the coagulation cascade, neutrophil recruitment, and the critical plasticity of macrophages (M1/M2 polarization). We discuss how the failure of these immune checkpoints leads to aseptic fibrous encapsulation rather than bone apposition, distinct from bacteria-induced peri-implantitis.

Keywords: *Osteoimmunology; Macrophage Polarization; Osseointegration; Foreign Body Reaction (FBR); Neutrophils; Titanium*

Introduction: The Paradigm Shift

The interface between a dental implant and bone is not static. It is a dynamic environment governed by the immune system. While bacterial challenge causes septic failure (peri-implantitis), a significant subset of early implant failures occurs due to aseptic factors-specifically, the body's inability to resolve the inflammation caused by surgical trauma and the introduction of a foreign material.

This review explores the concept that osseointegration is actually a form of chronic inflammation in perfect equilibrium. The immune system attempts to degrade the implant; failing to do so, it attempts to encapsulate it. The success of the implant depends on the immune system choosing "bony encapsulation" over "fibrous encapsulation".

Phase I: Protein adsorption and provisional matrix formation (Seconds to minutes)

Before cellular arrival, the physicochemical properties of the implant surface dictate the immune response.

- The Vroman effect: Within milliseconds of insertion, blood proteins compete for adsorption on the titanium surface. High-mobility proteins (albumin) arrive first, later replaced by high-affinity proteins (fibrinogen, fibronectin, vitronectin).
- Immune recognition: Immune cells do not bind to titanium; they bind to this protein layer via integrin receptors (e.g. \alpha_M\ beta_2).
- Complement activation: The alternative pathway of the complement system is activated by the titanium surface, generating C3a and C5a. These are potent chemoattractants that guide neutrophils to the site.

Phase II: The neutrophil response (Hours to days)

Neutrophils are the "first responders" essential for establishing a clean wound bed, but their prolonged presence is detrimental.

- Debridement: Neutrophils arrive to phagocytose necrotic bone debris and initial clots.
- NETosis: Neutrophils release Neutrophil Extracellular Traps (NETs)-webs of chromatin and proteases. While usually antimicrobial, excessive NETosis on rough implant surfaces in the absence of bacteria can cause collateral tissue damage and prolonged acute inflammation.
- The handoff: The most critical role of the neutrophil is to secrete chemokines (CCL2 and CCL3) to recruit monocytes (macrophage precursors).
- Clinical implication: If neutrophils fail to undergo apoptosis and be cleared by macrophages, the wound remains in a chronic "acute" state, preventing bone formation.

Phase III: Macrophage polarization and plasticity (Days to weeks)

Macrophages are the "architects" of osseointegration. They possess high plasticity, meaning they can change their phenotype based on micro-environmental signals.

The M1 phenotype (Pro-inflammatory)

- Inducers: IFN-\gamma, TNF-\alpha, and recognition of the foreign body.
- Cytokine profile: Secretion of IL-1β, IL-6, and TNF-\alpha.
- Function: These cytokines recruit additional immune cells and initiate osteoclastogenesis (bone resorption) to clear space around the implant thread.
- Duration: Dominant for the first 72-96 hours.

The M2 phenotype (Pro-healing):

- Inducers: IL-4, IL-10, IL-13.
- Cytokine profile: Secretion of IL-10, TGF-\beta (Transforming Growth Factor-beta), VEGF (Vascular Endothelial Growth Factor), and BMP-2 (Bone Morphogenetic Protein-2).
- Function: M2 macrophages suppress inflammation, promote angiogenesis (new blood vessels), and stimulate mesenchymal stem cells (MSCs) to differentiate into osteoblasts.

The "switch" determines fate

The transition from M1 to M2 is the rate-limiting step in osseointegration.

- Delayed Switch: Leads to fusion of macrophages into foreign body giant cells (FBGCs). These cells signal fibroblasts to create a collagen capsule (scar tissue)\right arrow clinical failure (Fibro-integration).
- Timely switch: Leads to recruitment of osteoblasts\right arrow clinical success (Osseointegration).

Surface characteristics as immunomodulators

The implant surface topography is not just for mechanical retention; it is an immunological trigger.

- Smooth/machined surfaces: Induce macrophage fusion (FBGCs) and fibrous tissue signaling. This leads to a higher risk of fibrous encapsulation.
- Microrough (SLA) surfaces: Increase the expression of anti-inflammatory cytokines (IL-10) and decrease pro-inflammatory ones (TNF-\alpha). This promotes the M1 \right arrow M2 switch, enhancing osseointegration.
- Nanotopography: Modulates cell shape. Macrophage elongation on nanostructures prevents pro-inflammatory activation, leading to superior osteoinduction.
- Hydrophilicity: Enhances adsorption of fibronectin, allowing faster macrophage adhesion and activation. This is associated with accelerated healing timelines (e.g. 3-4 weeks loading).

Osteo-immune crosstalk

The immune system and skeletal system share signaling molecules, a concept known as crosstalk.

- Osteoclast regulation: Macrophages and osteoclasts share the same lineage. The RANKL/OPG axis, typically associated with bone remodeling, is regulated by T-cells and B-cells near the implant surface.
- Angiogenesis-osteogenesis coupling: Bone cannot grow without blood supply. M2 macrophages secrete VEGF, which builds the vascular network required to transport minerals for calcification.

Conclusion

Osseointegration is an immunological defense mechanism where the body sequesters a foreign object (the implant) in bone rather than scar tissue. The clinician's ability to minimize trauma and the manufacturer's ability to modify surface topography are essentially methods of managing the Innate Immune Response. Future implant surfaces will likely be "bio-active" rather than "bio-inert," specifically designed to force macrophage polarization toward the M2 reparative phenotype immediately upon insertion [1-9].

Bibliography

1. Albrektsson T., *et al*. "Osteoimmunology: some implications for dental implants". *Journal of Dental Research* 93.12 (2014): 1195-1200.
2. Trindade R., *et al*. "Foreign body reaction to biomaterials: on mechanisms for buildup and breakdown of osseointegration". *Clinical Implant Dentistry and Related Research* 18.1 (2016): 192-203.
3. Takayanagi H. "Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems". *Nature Reviews Immunology* 7.4 (2007): 292-304.

4. Hotchkiss KM., *et al*. "Macrophage response to hydrophilic biomaterials regulates MSC recruitment and differentiation". *Biomaterials* 182 (2018): 202-215.

5. Hamlet S and Ivanovski S. "Inflammatory cytokine response to titanium chemical composition and nanoscale topography". *Clinical Oral Implants Research* 22.11 (2011): 1237-1245.

6. Vishwakarma A., *et al*. "Macrophage manipulation of cell sheet vascularization for bone regeneration". *Biomaterials* 104 (2016): 258-268.

7. Jhunjhunwala S., *et al*. "Neutrophil responses to sterile implant materials". *PLoS One* 10.9 (2015): e0137550.

8. Cooper LF. "The objective of selected surface design: from cell proliferation to tissue formation". *International Journal of Oral and Maxillofacial Implants* 24 (2009): 107-117.

9. Davarmanesh M., *et al*. "The immune system in osseointegration and peri-implantitis". *Journal of Periodontal Research* 55.5 (2020): 641-654.

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