ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

*International Journal of Dental Science and Innovative Research (IJDSIR)*

*IJDSIR : Dental Publication Service*

*Available Online at:www.ijdsir.com*

*Volume – 8, Issue – 6, November – 2025, Page No. : 247 - 257*

# Biomimetic Functionalization of Dental Implant Surfaces: A Concise Review on Material Science and Biological Perspectives

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**Citation of this Article:** Sri Jhansi Meetakoti, D. Krishna Manohar, Surapaneni Hemchand, Tripuraneni Sunil Chandra, "Biomimetic Functionalization of Dental Implant Surfaces: A Concise Review on Material Science and Biological Perspectives", IJDSIR- November – 2025, Volume – 8, Issue – 6, P. No. 247 – 257.



**Type of Publication:** Review Article

**Conflicts of Interest:** Nil

## Abstract

Numerous treatment strategies exist for addressing bone defects, with biomimetic approaches being fundamental to many of these methods. Implant dentistry has emerged as a significant speciality within the field of dentistry. The primary objective of modern dental care is to restore patients to a normal state of function, aesthetics, comfort, speech, and overall health, whether through caries removal or the replacement of one or more teeth. The distinct advantage of implant dentistry lies in its ability to achieve these goals regardless of factors such as atrophy in the stomatognathic system or the presence of disease or trauma.[1] The process of osseointegration, which is essential for the dental implant's success, has been impacted by both the implant's design and the properties of its surface. Once an implant is placed, the surface characteristics are crucial for its integration. In order to improve bioactivity along with osteo-conductivity of the implant, several strategies have been developed, including the application of biomimetic coatings on titanium and its alloys. These coatings stimulate endothelial cell differentiation and can promote vascularization in the cortical bone, thereby contributing to improved bone health and implant success.

**Keywords:** Aesthetics, Bone Homeostasis, Calcitonin Dentistry, Osteoconduction

## Introduction

Otto Schmitt coined the term "biomimetic" in the 1950s, that means "to imitate life." The growth of this concept can be attributed to significant advancements in biomaterial technologies and implant procedures. As a result, there are rising expectations concerning the performance and longevity of implants.[2] The field has evolved from a focus on bioinclusion to the bioactive paradigm, which emphasizes surface modifications which stimulate particular biological responses in the tissues surrounding it.

Titanium's advantageous bulk and surface qualities have made it the preferred material for a variety of load-bearing applications. A key current difficulty in the field is developing titanium surfaces that foster a strong interface with bone and support its continuous regeneration.

**Bone Metabolism: The Cycle of Bone Growth and Resorption** Bone homeostasis involves a series of coordinated cellular and molecular processes. Osteoblasts, which create new bone, and osteoclasts, which degrade bone tissue, are the primary cells that are involved in bone metabolism. The structural integrity of bone and the adequate calcium supply relies on the close cooperation of such cells, as well as other cell populations, such as immune cells, found at bone remodelling sites. Proper bone metabolism is regulated by intricate signaling pathways and control mechanisms that ensure balanced growth and differentiation.[2] Several hormones are integral to these processes, including PTH (parathyroid hormone), steroids, growth hormone, vitamin D, along with calcitonin. Additionally, bone marrow- derived soluble cytokines and growth factors, such as RANKL, M-CSF, the VEGF family, and the IL-6 family, similarly play key roles. Through these mechanisms, the body maintains the necessary calcium levels for normal physiological functions. As such, bone regeneration is not simply an occasional repair of damaged bones but rather a continuous, ongoing process within a healthy body. Osteoclasts resorb bone surface, and osteoblasts follow by depositing new bone, all in response to the appropriate signals.

**Bone Regeneration and the Role of the Basic Multicellular Unit (BMU)** Cells involved in bone regeneration function together as a unit called the BMU. BMU is defined by the period of bone regeneration as well as performs a crucial role in sustaining the cycle of bone growth and resorption throughout life.

Osteoinduction, osteoconduction, and osseointegration are distinct phenomena in bone healing procedures. Osteoinduction refers to stimulation of new bone formation, a key component of normal bone healing, particularly following fractures or implants. Although osteoinductive implants may facilitate this process, they are not essential for bone induction.[3] On the other hand, osteoconduction describes the bone's ability to grow along a surface, influenced by both biological factors and the body's response to the foreign substances. While osteoconductive responses may be temporary, osseointegration ensures lasting bone attachment, providing long-term stability and anchorage for implants.

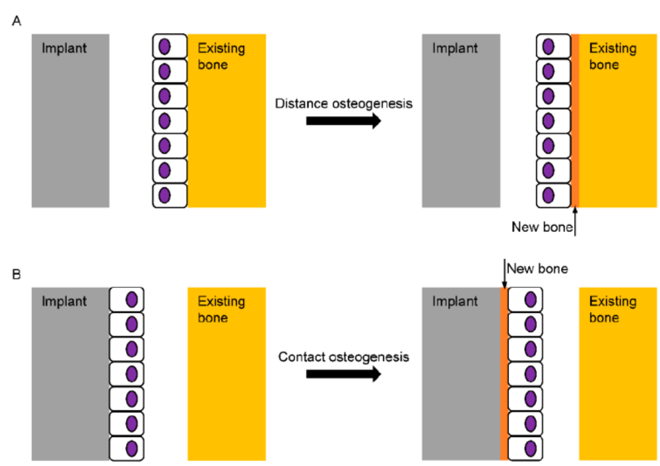



Figure 1: Schematic representation of Distance Osteogenesis & Contact Osteogenesis

**Biomimetic Agents**

Biomimetic agents include a variety of materials and compounds that mimic natural bone properties to support bone regeneration and healing. These include:

- Bioceramics, such as hydroxyapatite (HA), which closely resemble the mineral component of bone.
- Calcium phosphate phases, which are crucial for bone mineralization and provide a supportive structure for bone growth.
- Bioactive proteins, including bone morphogenic proteins, which perform a substantial role in the bone formation, as well as Type 1 collagen, an essential structural protein in the bone tissue.
- RGD peptide sequences, which facilitate cell attachment and promote tissue integration.
- Ions, like fluoride, which contribute to bone mineralization and strength.
- Polymers, such as chitosan, that support bone regeneration by interacting with cells and enhancing tissue repair.

1. **Bioceramics**

Calcium phosphate salts are commonly utilized in dentistry as bioceramics. The hydroxyapatite's (HA) incorporation onto surface of titanium implants represents an early enhancement that promotes faster osseointegration. HA can be applied to implants using techniques such as electrophoresis, plasma spraying, or ion beam deposition. Currently, a widely used method for the deposition of HA is through physiological processes, which include electrolytic deposition or immersing implants in simulated body fluid (SBF). SBF, prepared under specific conditions, is rich in calcium, phosphorus, and other essential elements. Over time, gradual precipitation forms a layer of phosphate crystals that measures between 30 and 50 micrometers. Bioceramic-coated dental implants are a promising treatment option due to their excellent biocompatibility and long-term success rates.

2. **Bioactive Proteins** Urist was the first to identify a group of proteins with osteoconductive properties, which later became known as bone morphogenic proteins (BMPs). These proteins, which include both intra- and extraosseous types, can be implanted at various sites, such as muscle or subcutaneous tissue, to promote bone formation and healing.

**Growth Factors**: Low-molecular-weight polypeptide proteins are Cytokines (<80 kDa) with pleiotropic effects. Platelet-rich plasma (PRP) has gained attention for its high concentration of growth factors (GFs). These factors, that include TGF- β (transforming growth factor-beta) and platelet-derived growth factors, perform a vital role in enhancing regeneration. In this process, the insulin-like growth factors are also very important. However, PRP coatings on implants present challenges, such as the short half-life of growth factors, which can conflict with the sustained release required for effective biomimetic applications.

**Type I Collagen**: The most prevalent protein in the human body, collagen is essential for tissue regeneration and repair since it is present in both soft along with hard tissues and has dimensional stability. As a result, it has been considered for use in implant surface coatings. Type I collagen, produced by osteoblasts, serves as a scaffold for the development of bones. For implant surface coatings, Type I collagen is regarded as a biological mimic of the extracellular matrix (ECM), providing essential support for bone regeneration.

**RGD Peptide**

RGD peptide sequence (arginine-glycine-aspartic acid) has been found in numerous ECM proteins and is known to bind strongly to integrins, facilitating cellular adhesion and signaling. Research has shown that human osteoblast-like cells adhere more readily to implant surfaces coated with RGD peptides, promoting early osseointegration. This makes RGD peptides a promising biomimetic agent for enhancing selective osteoblast binding to implant surfaces, thereby supporting more effective bone integration.

3. **Fluoride**

Fluoride-treated implants are considered biomimetic agents due to their ability to promote the formation of fluorapatite, which enhances interaction among the implant along with surrounding bone tissue. The process entails stimulating osteoblast proliferation along with activating alkaline phosphatase activity, both of which contribute to improved bone formation and integration with the implant.

4. **Polymers – Chitosan**

Chitosan is a natural polysaccharide polymer composed of glucosamine and N- acetylglucosamine copolymers. When used in bone tissue applications, chitosan has been shown to function as an efficient scaffold for the osteoblasts, facilitating the deposition of the extracellular matrix. It also supports the differentiation of preosteoblastic cells and exhibits moderate osteoconductive properties, aiding in the bone formation process.[4]

**Biomimetic Surface Properties:** A number of factors affect dental implant’s long term success, with the surface characteristics of the implants being crucial to their durability.

**Topography**

Surface topography significantly impacts protein adsorption along with cell adhesion. The scale of nanotopography, characteristically varying from 1-100nm, plays a key role in this process. Surface topography is recognized as a crucial biological factor influencing cell proliferation, structure, alignment, and function. It is also considered one of the most important determinants for effective cell adhesion.

**Roughness**

By enhancing bone-to-implant contact (BIC), rough surfaced implants have a beneficial impact on the response of osteogenic along with inflammatory cells. This leads to improved clinical outcomes, including rapid healing and the probability of earlier implant loading.

To assess surface roughness of implants, three most frequently utilized techniques are contact profilometry, optical profilometry, and atomic force microscopy.

**Wettability**

The wettability of biomaterial surfaces is influenced by surface characteristics for example chemical composition along with topography. Four essential components of the biological system may be impacted by these characteristics: 1) the behavior of the proteins along with other macromolecules on the surface, 2) the interaction of hard and soft tissues with the surface, 3) bacterial adhesion as well as biofilm formation, and 4) the rate of clinical osseointegration. Hydrophilic surfaces, in particular, enhance cell and protein adhesion, facilitate interactions with body fluids, additionally might accelerate processes of tissue healing by improving cell and tissue integration.[4]

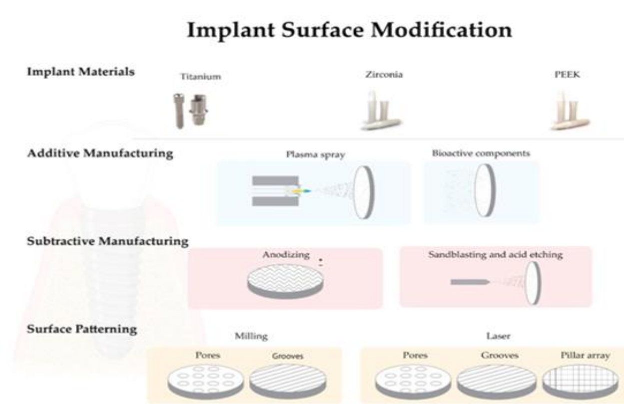
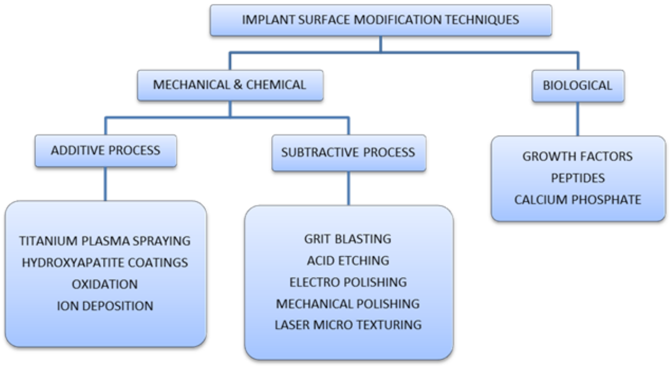



Figure 2: Implant Surface Modifications




Flowchart 1: Classification of Implant Surface Modifications

**Methods of Surface Modification:** Methods of surface modification are able to be categorized as either subtractive or else additive. Biomaterial is removed from the implant surface utilizing subtractive processes, that involve sandblasting, acid etching, and anodizing. In contrast, additive methods involve the application of additional materials to implant surface, such as plasma spraying, ion deposition, and hydroxyapatite or else calcium phosphate coatings, which enhance the implant's properties.

**Biomimetic Surface Modifications**

**Additive Manufacturing**

Plasma spraying is a commonly used additive manufacturing technique for modifying titanium surfaces, known as TPS (titanium plasma spray). Surface roughness has been enhanced through this process by depositing hydroxyapatite onto the implant surface. After being put into a high-temperature plasma torch, the particles are projected onto the implant surface, where they condense and combine to create a coating. To improve the coating's durability, surface is typically sandblasted before final coating is applied. The thickness of the coating can range from a few micrometers to several millimeters.[5]

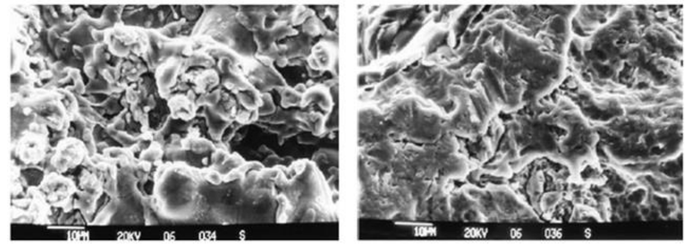


Figure 3: Surface Roughness of Plasma Sparyed Implant

**Addition of Bioactive Components:** The biomaterial surface's chemical properties significantly influence cell-biomaterial interactions, which are crucial for osseointegration. HA and βTCP (beta- tricalcium phosphate) are often utilized as bioactive coatings to enhance osteoblast differentiation, biocompatibility, along with osseointegration. In contrast to pure biomaterials, bioactively modified titanium and zirconia surfaces have been observed in vitro to lessen fibroblast cell adhesion, viability, as well as proliferation. Additionally, these bioactive coatings have lower fracture toughness (varying from 0.28-1.41MPa.m1/2) and tensile strength (<51MPa).

To overcome these limitations a novel coating technique has been developed that draws inspiration from natural biomineralization. Utilizing SBF (simulated body fluids), calcium phosphate crystals are deposited upon titanium surfaces creating a coating that can be left at room temperature.

Furthermore, as an osteoinductive approach, the incorporation of growth factors that include TGF-ß and BMPs has been investigated. While encouraging outcomes have been observed in the bone healing, primary limitation of these growth factors is their rapid, non-sustained release.[5]

**Biomimetic Surface Modifications**

**Subtractive Manufacturing**

**Anodizing**

Anodizing involves modifying the titanium surface by utilizing strong acids, for example, phosphoric acid

($H_3PO_4$), hydrofluoric acid (HF), sulfuric acid ($H_2SO_4$), or else nitric acid ($HNO_3$), that enhance surface roughness as well as facilitate the formation of an oxide layer. This oxidation process is commonly used in products from well-known brands like TiUnite and Nobel Biocare in Sweden. Dental implants with anodized surfaces have been reported to have higher BIC than those with machined surfaces in both human and animal trials.

**Blasting and/or Acid Etching**: Another technique to increase surface roughness is sandblasting, where titanium oxide or alumina particles are propelled at high speed onto the implant surface. After blasting, powerful acids, for example, $H_2SO_4$, $HNO_3$, HF, or else HCl, are employed to eliminate oxide impurities. This process results in a slightly roughened surface with a Sa value of around 1 µm, accompanied by an alteration in the implant surface's chemical composition following acid etching.

**Biomimetic Surface Patterning:** Grooved and micro textured surfaces offer directional cues that guide osteoblast morphogenesis, promoting alignment in the preferred direction through a process known as "contact orientation." This can enhance the development of bone around the implant.[5]

**Milling**

Milling is a process used to modify the original shape of materials, allowing for an assessment of their machinability. Factors such as the type of cutting tools used, the surface finish achieved, nature of the chips formed, and required machining power all influence the final surface characteristics. The imperfections left along milled surfaces can facilitate the attachment of osteogenic cells, promoting bone deposition and creating a robust bone-to-implant interface.

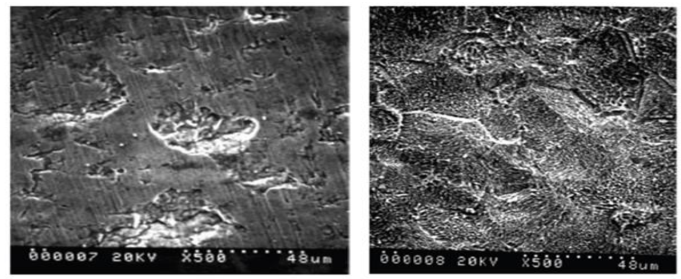



Figure 4: Surface Roughness of Milled Implant

**Laser**

Nd: YAG and CO2 lasers are frequently employed to create textured surfaces, particularly for standardizing zirconia surfaces. Laser technology utilizes concentrated energy to heat, melt, and modify materials, resulting in surface textures at macro, micro, and nano scales. This process enhances the surface roughness of zirconia implants while preserving the crystalline tetragonal phase, ensuring surface remains clean along with homogeneous.

Table 1: Studies on Surface Treatment of Implants

| Table 1: Studies on Surface Treatment of Implants | | | | |
|---|---|---|---|---|
| Author | Type of Implant | Surface Treatment | Findings | AVG. Roughness Ra (µm) |
| Knabe et al.[19] | CP-Ti ASTM-F67 | Plasma spray Ti coating, acid etching, and sandblasting, HA coating | All implants except HA coating surface showed good growth cells. | Ti coating 3.43 ± 0.63 HA coating 2.07 ± 0.36 |
| Depprich et | ZrO2 | Acid etching | Acid etched surface shows | 0.598 |

| | | | | |
|---|---|---|---|---|
| al.[20] | Ti | Acid etching | similar properties of osseointegration with titanium implant. | 1.77 |
| Hung et al.[21] | CP-Ti (Ti-6Al-4V ELI, ASTM-F136) | Plasma sprayed hydroxyapatite (HA) | Treated implants indicate high biocompatibility for bone regeneration of titanium implants | Sa 9.36 |
| Eom et al.[22] | Ti | Blasting HA<br>Blasting and dual acid etching<br>(3) hybrid-type coating with HA and blasting | Hybrid type coating shows higher bone<br>implant contact and removal torque value<br>(259.9 ± 6.2Ncm) than other surfaces. | 1.2–1.8<br>2.5–3.0<br>3.0–3.5 |
| Aparicio et al.[23] | CP-Ti<br>ASTM B348 | Acid etching<br>Grit blasting<br>Grit blasted and alkaline etched + thermos chemical treatment | Blasted and alkaline etched plus thermal formed rough and bioactive surface lead to accelerate bone tissue regeneration and increased mechanical retention in the bone. | 1.69 ± 0.1<br>4.74 ± 0.2<br>4.23 ± 0.2 |
| Ban et al.[24] | CP-Ti | Acid etching with variable parameter (temperature and time) | Surface roughness increased as temperature and time increased. Weight loss increased linearly with time and temperature | 0.44–3.51 |
| Yang et al.[25] | Ti | YSZ plasma spray<br>Acid etching | After acid etching, the Ti surface is roughened and may enhance the osseointegration. | 8.68 ± 0.37 |
| Al-Radha et al.[26] | Ti | Blasting with ZrO2 Blasting with ZrO2 and acid etching (SLA) | Blasted ZrO2 surface showed a very good effect on adhesion reducing almost similar to pure ZrO2 properties. | 0.158 ± 0.003<br>0.150 ± 0.005 |
| Simon et al.[27] | cpTi | Ti plasma spray | Surface roughness by Ti coating may optimize the osseointegration and enhance the clinical function. | 4.4 ± 0.37 |

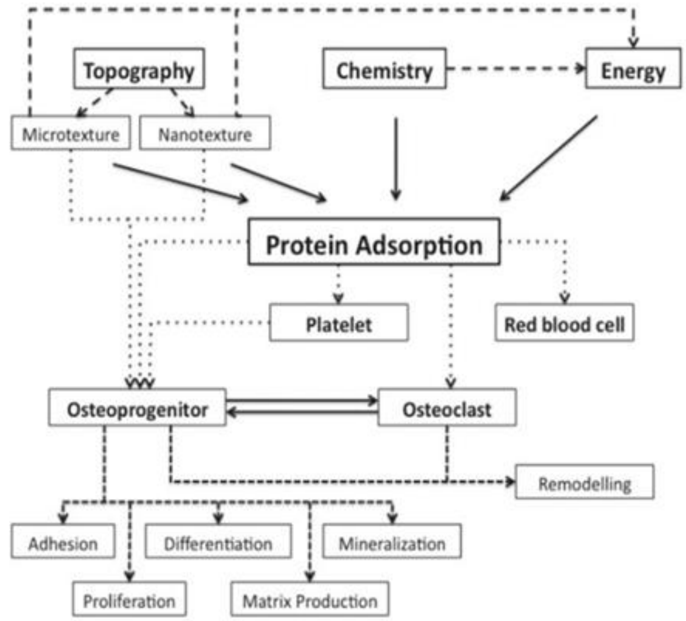
**The Evolution of Titanium-Based Implants for Bone Regeneration: From Bio- Inertness to Bio-Activeness:**

The physicochemical characteristics of the passive oxide layer that naturally develops on the titanium surface are primarily responsible for titanium implants' ability to successfully stimulate bone formation. Because of titanium's strong oxygen solubility, this protective layer forms in just a few seconds after being exposed to environmental factors. Titanium implant surface modifications have been shown to enhance healing and stimulate increased bone formation.

However, titanium implants interact with both bone tissue along with soft tissues, especially when placed in areas like the oral cavity, where they establish a transmucosal connection. Compared to the endosseous implant body, these soft tissues have quite different healing requirements. It is essential to properly manage the soft tissues around implants to avoid bacterial colonization, which can impair the implants' ability to heal initially and survive over time.

Consequently, factors that include design of coronal portion of the implant, as well as variations in surface topographies and compositions, have become key areas of investigation. The equilibrium between immunomodulation and osseointegration is another vital topic that is receiving more attention. Recent studies have highlighted how inflammatory cells can influence fate of human mesenchymal stem cells (MSCs) by the exosomes release. Several strategies are now being explored to replicate the physiological extracellular environment as well as modulate the host immune response for optimizing implant success.[5,6,7]

**Surface Characteristics and Protein Immobilization on Implants:** Several surface characteristics perform a critical role in determining stability, orientation, along with conformation of protein immobilization mechanisms on implant surfaces. The primary factors that govern these interactions are the surface's topology and chemistry. These fundamental properties are crucial in regulating how proteins interact with the surface, influencing efficiency of protein immobilization and ultimately the implant's success.[7]




Flowchart 2: Impact of submacron surface characteristics of the implant on the osteogenic response

**Nanoporous Titanium Implant Surface Promotes Osteogenesis by Modulating Osteoclastogenesis via Integrin β1/FAKpY397/MAPK Pathway:** The nanoporous surface of titanium implants has been shown to significantly accelerate early bone formation in vivo. Additionally, this surface modification enhances macrophage recruitment while reducing osteoclast formation. The underlying regulatory mechanisms, however, remain largely unclear. The presence of numerous nuclei and positive expression of TRAP (tartrate-resistant acid phosphatase) are characteristics of osteoclast differentiation, that is usually produced from monocyte/macrophage progenitors in the presence of RANKL (receptor activator of nuclear factor-kappa B ligand).[7,8]

Given that osteoclast differentiation occurs from the monocyte/macrophage lineages under RANKL influence, it is plausible that there are shared regulatory pathways between macrophage polarization and osteoclastogenesis.

Focal adhesions, which are complexes of proteins such as integrins, talin, and vinculin, connect the cytoskeleton to the ECM and are involved in mediating cellular signaling. These complexes may play a key role in modulating osteoclastogenesis and osteogenesis on nanoporous surfaces.

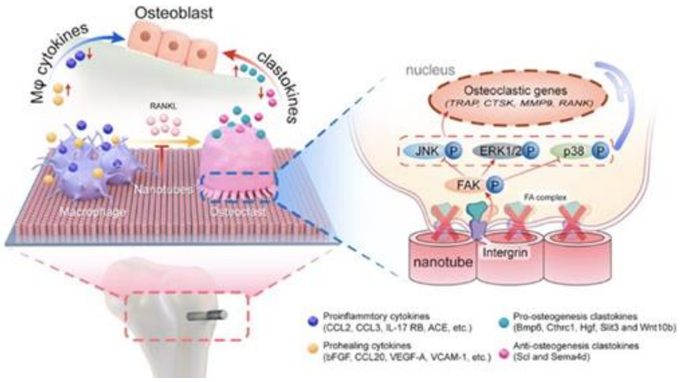



Figure 5: A schematic diagram representing the role of the MNT5 surface in promoting osteogenesis by modulating monocyte/macrophage lineage

**Nanopatterned Implant Surfaces and Their Impact on Osseointegration:** The distribution and phenotype of monocyte/macrophage lineage cells may be changed by different nanopatterns on implant surfaces, that can have a substantial impact on osseointegration process. For instance, Karazisis et al. found that tissues surrounding nanoscale implants had lower recruitment rates of CD68-positive macrophages than tissues with polished surfaces.[9,10]

In our findings, both micro- and nanotopographies significantly reduced osteoclast TRAP activity along with the osteoclastogenic markers expression in contrast to polished or else micropitted surfaces. This effect might be because of the synergistic interaction between micro- and nano-scale surface roughness. Furthermore, Gross et al. demonstrated that hydroxyapatite coatings applied via spraying induced stronger osteoclast absorption activity than polished hydroxyapatite coatings. The variation in topographical regulation might stem from differences in culture conditions, experimental duration, and the complexity of how cells perceive the substrate.[9,11]

**Nanotube Diameter and Its Role in Osteoclast Differentiation and Osteogenesis:** It is not advantageous to substantially suppress osteoclast differentiation in order to promote osteogenesis, even if our findings indicate that nanotubes with greater diameters, for instance, MNT20, have a stronger ability to block osteoclastic differentiation. Moderate osteoclast differentiation is actually essential for coupling osteogenesis. Consequently, the better nanotopography for promoting bone regeneration is MNT5.[12]

## Conclusion

In summary, our conclusions highlight the substantial role of nanoporous titanium surfaces in modulating clastokines expression from the osteoclasts as well as cytokines from macrophages. These changes in the secretory profiles of key immune and bone cells are crucial in fostering an environment that promotes accelerated bone regeneration. The enhanced osteogenic response, coupled with the modulation of osteoclastogenesis and macrophage polarization, suggests that nanoporous surfaces play a vital role in optimizing osseointegration and tissue healing [13] [14]. By fine-tuning the interactions between these cells, nanoporous titanium surfaces could represent a promising strategy for improving the long-term success of dental implants, facilitating not only faster recovery but also more stable bone-implant integration.[13,15]

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