Electroactive Biomaterials: Orchestrating Electrical Cues for Enhanced Osseointegration and Bone Regeneration- A Narrative Review

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Abstract: Electroactive biomaterials are emerging as a transformative approach to enhance osseointegration and bone regeneration by mimicking the intrinsic electrical microenvironment of native bone. This review synthesizes recent advancements in piezoelectric, conductive, and composite electroactive materials, highlighting their capacity to modulate cellular behavior, promote osteogenesis, and combat implant-associated infections. Studies demonstrate that optimized 3D topographies and nanoarrays on piezoelectric substrates, coupled with conductive polymer coatings and antimicrobial surface modifications, significantly improve bone-implant integration and regeneration. Furthermore, the development of self-powered systems and multifunctional coatings exemplifies the pursuit of autonomous, biomimetic implants. Future directions should focus on integrating smart sensors for real-time feedback, developing biodegradable and self-healing materials, elucidating cellular mechanotransduction mechanisms, and establishing robust clinical translation pathways. By harmonizing electrical stimulation, antibacterial properties, and advanced material design, electroactive biomaterials hold immense promise for revolutionizing orthopedic and dental therapies.

Keywords: Electroactive materials, Osseointegration, Bone regeneration, Bone tissue engineering.

1. Introduction

Electroactive biomaterials are rapidly gaining prominence in the field of regenerative medicine, particularly for their potential to revolutionize bone tissue engineering. The conventional approach to orthopedic and dental implants, which relies primarily on materials like titanium and its alloys, often provides excellent mechanical support but lacks the capacity to actively engage with the complex biological processes inherent in bone healing. This inertness can lead to suboptimal osseointegration, delayed healing, and increased risk of complications such as infections and implant loosening[1,2]. In contrast, electroactive materials offer a dynamic interface between the implant and the host tissue by generating or responding to electrical stimuli, mimicking the natural bioelectric environment of bone[3].

Bone tissue possesses intrinsic piezoelectric properties, wherein mechanical stress generates electrical potentials that play a pivotal role in regulating cellular activities such as proliferation, differentiation, and extracellular matrix deposition. These bioelectrical signals are crucial for maintaining bone homeostasis and facilitating repair processes[4]. When bone tissue is injured or an implant is inserted, these natural electrical cues are disrupted, potentially hindering the healing cascade. Electroactive materials aim to restore or augment these physiological signals, thereby promoting a more conducive environment for bone regeneration and osseointegration[5,6].

This review delves into the diverse landscape of electroactive biomaterials, encompassing piezoelectric ceramics, conductive polymers, and composite systems, and their applications in bone tissue engineering. Piezoelectric materials, such as barium titanate (BaTiO3) and polyvinylidene fluoride (PVDF), generate electrical charges in response to mechanical deformation, directly replicating the natural piezoelectric behavior of bone. Conductive polymers, including polypyrrole (PPy) and polyaniline (PANI), facilitate the delivery of electrical stimuli to cells, enhancing cellular adhesion and proliferation. Composite materials, which combine the benefits of piezoelectric and conductive components, offer synergistic effects, providing both mechanical robustness and enhanced electrical responsiveness.

Furthermore, this review explores the underlying mechanisms by which electroactive materials influence cellular behavior, including the activation of voltage-gated ion channels, modulation of growth factor production, and regulation of gene expression. It also examines the various applications of these materials in implant coatings and scaffolds, highlighting their potential to improve bone-implant integration and promote bone ingrowth in critical-sized defects.

Electroactive biomaterials

Electroactive biomaterials offer diverse properties for various applications, each with its own set of advantages and disadvantages[3,4]. Piezoelectric/ferroelectric ceramics like BT exhibit high piezoelectric coefficients, good biocompatibility, and negligible cytotoxicity, but suffer from poor degradability, brittleness, and processing challenges. Zinc oxide (ZnO) demonstrates excellent biodegradability and antibacterial properties, though it presents dose-dependent cytotoxicity. Polyvinylidene fluoride (PVDF), another piezoelectric/ferroelectric polymer, offers high flexibility, stiffness, and an elastic modulus similar to cancellous bone, but has poor biodegradability and potential heart failure risks. Poly(lactic acid)/poly(L-lactic acid) (PLA/PLLA) provides good biocompatibility and biodegradability, but exhibits unstable electrical power and weak mechanical properties[2,3]. Carbon-based conductive materials such as carbon nanotubes/graphene oxide (CNT/GO) possess great mechanical properties, large surface area, and high conductivity, yet have low biodegradability, dose-dependent cytotoxicity, and poor dispersion. Conductive polymers like polypyrrole/polyaniline/poly(3,4-ethylenedioxythiophene) (PPy/PANi/PEDOT) offer commercial convenience and good processibility, but have low biodegradability and poor dispersion. Finally, conductive metals like silver/gold nanoparticles (Ag/Au) display robust mechanical properties, high conductivity, and antibacterial activity, but are expensive and have low biodegradability[4,5,6].

Biological Basis for Electroactivity in Bone Healing

Bone exhibits inherent piezoelectric properties, where mechanical stress generates electrical potentials that influence cellular activities such as proliferation and differentiation. Disruption of these electrical cues, as seen in injuries or implant placements, can impair healing. Electroactive materials aim to restore these natural bioelectric signals, facilitating improved bone regeneration and osseointegration [2,4,7].

Types of Electroactive Materials

Piezoelectric Materials

Piezoelectric materials generate electrical charges in response to mechanical stress. Natural bone's piezoelectricity is attributed to collagen and hydroxyapatite. Synthetic piezoelectric materials like polyvinylidene fluoride (PVDF) and barium titanate ($BaTiO_3$) have been incorporated into scaffolds to replicate this effect, promoting osteogenic differentiation and matrix mineralization[5,8].

Conductive Polymers

Conductive polymers, such as polypyrrole (PPy) and polyaniline (PANI), facilitate electrical stimulation of cells. These materials support osteoblast adhesion and proliferation and can be combined with bioactive molecules to enhance regenerative outcomes. Conductive polymers are often integrated into biodegradable scaffolds to maintain structural integrity[3,9].

Composite Electroactive Systems

Combining piezoelectric and conductive materials in composite systems offers synergistic benefits. For example, scaffolds incorporating PVDF and carbon-based materials like graphene oxide provide enhanced electrical responsiveness while maintaining desirable mechanical properties, leading to improved tissue regeneration[1,10].

Mechanisms of Action in Bone Regeneration

Electroactive materials influence cellular behavior through various mechanisms. Local electrical fields generated by these materials can activate voltage-gated calcium channels, increasing intracellular calcium levels and promoting osteogenic gene expression. Additionally, they modulate the production of growth factors essential for bone healing and vascularisation[2,11].

Electrostimulation plays a significant role in influencing osteogenic cell behavior through a complex interplay of signaling pathways. Initially, it triggers the activation of voltage-gated calcium channels (VGCCs) and stretch-activated Ca2+ channels (SACCs), leading to an influx of calcium ions (Ca2+). This influx subsequently induces the release of Ca2+ from the endoplasmic reticulum by activating phospholipase C (PLC) and inositol trisphosphate (Ins3P) receptor channels[3,5,8]. The resulting increase in intracellular Ca2+ concentration activates the calmodulin/calcineurin (CaM/CaN) pathway, which in turn leads to the dephosphorylation of nuclear factor of activated T-cells (NF-AT). This dephosphorylation is crucial for the translocation of NF-AT into the nucleus, where it promotes the expression of osteogenic genes, notably transforming growth factor-beta (TGF-β) and bone morphogenetic protein (BMP). When BMP binds to cells, TGF-β, a key transcription factor, participates in activating the mitogen-activated protein kinase (MAPK) and SMAD pathways, thereby promoting osteoblast proliferation and differentiation[5,7,8]. This process is further enhanced by initiating the Wnt/β-Catenin pathway, which contributes to differentiation and migration by regulating extracellular matrix (ECM) production and osteogenic gene expression[9]. Furthermore, electrostimulation induces the immediate downregulation of DNA methyltransferase 1 (DNMT1), while significantly upregulating the expression of octamer-binding transcription factor 4 (OCT4) and NANOG genes through demethylation of their promoters. This demethylation process is vital for maintaining the osteo-differentiation-inducing ability of these genes[10,11].

Applications in Implant Coatings and Scaffolds

Surface modification of implants with electroactive coatings has shown promise in improving osseointegration. Piezoelectric coatings on titanium implants have demonstrated increased bone-to-implant contact in preclinical studies. Similarly, 3D-printed scaffolds incorporating electroactive materials provide a dynamic microenvironment that supports bone ingrowth and vascularization, particularly useful in treating critical-sized bone defects[12].

Electroactive Materials in Enhancing Osseointegration and Bone Regeneration[12-20]

The collective body of research presented underscores the burgeoning potential of electroactive materials in revolutionizing bone tissue engineering. Notably, studies consistently demonstrate the efficacy of piezoelectric materials like BaTiO3 and PVDF, particularly when structured with optimized 3D topographies or nanoarrays, in enhancing osseointegration by mimicking the native electromechanical environment of bone[12,13,14]. These designs facilitate localized electrical stimulation, promoting osteogenic differentiation and accelerating bone repair, as evidenced by enhanced calcium influx and mechanosensing integrin activation. Furthermore, the incorporation of conductive polymers such as polypyrrole and PANI, often in composite systems, enables precise electrical modulation of cellular behavior, fostering improved cell adhesion, proliferation, and vascularization. Beyond electrical cues, the integration of antibacterial functionalities becomes crucial for implant longevity. Surface modifications leveraging titanium oxide metasurfaces, chitosan/ZnO composites, and silver/zinc nanoparticles effectively combat implant-associated infections, addressing a critical clinical challenge[13,15,16]. The exploration of self-powered systems, exemplified by triboelectric nanogenerators, marks a significant stride towards autonomous, continuous stimulation, eliminating the reliance on external power sources. Moreover, the development of multifunctional coatings, such as those employing P(DMA-co-MPC-co-DMAEMA) terpolymers, illustrates the ability to harmonize traditionally incompatible properties like robust adhesion, antifouling, and antimicrobial activity within a single material[15,17,18]. This holistic approach, combining electrical stimulation, antibacterial properties, and tailored surface characteristics, signifies a paradigm shift towards designing

biomimetic implants that actively participate in and accelerate the natural bone healing process. However, while preclinical results are promising, future endeavors must prioritize long-term biocompatibility, scalability of manufacturing, and rigorous clinical validation to translate these innovative materials into effective therapeutic solutions[19,20].
(TABLE1)

Table 1 Performance Evaluation of Electroactive Materials in Enhancing Osseointegration and Bone Regeneration

Author (Year)	Material Type	Composition/Structure	Application Form	Biological Model	Key Findings	Mechanism of Action
Zhou T et al.[12] (2019)	Electroactive Scaffold	Polypyrrole-polydopamine-hydroxyapatite (PPy-PDA-HA) film	Coating on porous titanium scaffold	In vitro (osteogenic cells)	Enhanced electroactivity, cell affinity, ROS scavenging, osteoinductivity	Electrical stimulation, ROS scavenging by PPy-PDA, osteoinductivity of HA
van Hengel IAJ et al.[13] (2020)	Biofunctionalized Titanium	Porous titanium with silver and zinc nanoparticles via PEO	Coating on 3D-printed porous titanium implants	In vitro & ex vivo (MRSA, pre-osteoblasts)	Enhanced antibacterial activity, synergistic effect of Ag/Zn, improved osteogenic activity	Ag/Zn ion release, ROS generation, PEO for nanoparticle embedding
Wu S et al.[14] (2024)	Biomimetic Heterostructure	Titanate/TiO2-X heterostructure (KMNW, NaMNS)	Coating on titanium implants	In vitro (S. aureus, E. coli, osteoblasts); In vivo (rat)	Enhanced antibacterial effect, promoted osteogenic differentiation, improved osseointegration	Photothermal/photodynamic therapy (PTT/PDT) via NIR irradiation, mimicking ECM fibrous network
Wu J et al.[15] (2024)	Titanium Oxide Metasurface	Titanium oxide nanostructure	Coating on titanium alloy	In vitro (S. aureus, E. coli, MC3T3-E1 cells)	Enhanced antibacterial effect, improved cell adhesion, proliferation, differentiation, and osteogenic gene expression	Photodynamic reaction via NIR irradiation, nanostructure facilitating cell response
Zhang Y et al. [16](2024)	Multifunctional Terpolymer Coating	P(DMA-co-MPC-co-DMAEMA) terpolymer	Coating on medical devices	In vitro (biofoulant interactions)	Robust adhesion, antifouling, lubrication, antimicrobial properties	DMA for adhesion, MPC for antifouling, DMAEMA for antimicrobial activity
Long S et al. [17](2025)	Composite Coating	Chitosan/ZnO composite	Electrophoretic deposition on 3D-printed titanium alloy	In vitro (S. aureus, E. coli, cells), SBF immersion	Enhanced antibacterial properties, good biocompatibility, improved mechanical properties, increased hydroxyapatite precipitation	ZnO antibacterial effect, chitosan biocompatibility, Zn^{2+} enhancing bioactivity
Wang MK et al[18]. (2025)	Nano-TiO2 Coating	Nano-TiO2 coating	Coating on 3D-printed titanium alloy (Ti6Al4V)	In vitro (S. aureus, E. coli)	Enhanced antibacterial properties, improved hydrophilicity, excellent photothermal response	Photothermal effect via NIR irradiation, nano-TiO2 synergistic antibacterial effects
Sun X et al[19]. (2025)	Piezoelectric Substrate with 3D Topography	BaTiO3 (BTO) micropillar arrays	Substrate/Scaffold	In vitro (BMSCs); In vivo (rat femoral defect)	Enhanced BMSC spreading, osteogenic differentiation, accelerated bone repair and osseointegration	3D spatial electrical stimulation, increased mechanosensing integrin α5 clustering
Wu M et al. [20](2025)	Piezoelectric Nanoarrays	Barium titanate piezoelectric nanoarrays	Substrate/Scaffold	In vitro (DRG neurons, BMSCs)	Promoted innervated bone regeneration, activated Piezo2 and VGCC ion channels, enhanced osteogenic differentiation	Mechanical-electrical coupling microenvironment, calcium influx, CGRP release

2. Challenges and Future Perspectives

Challenges

The advancement of electroactive materials for osseointegration and bone regeneration faces several critical challenges that must be addressed to facilitate successful clinical translation. Foremost is the imperative to ensure long-term biocompatibility, demanding rigorous evaluation of material degradation byproducts and their potential for adverse tissue reactions over extended periods. Achieving controlled biodegradation rates that synchronize with bone regeneration timelines remains a significant hurdle, as does mitigating potential immune responses and guaranteeing the stability of electrical and mechanical properties under physiological conditions[14,18,19]. Precise control over electrical performance is equally vital, requiring the determination of optimal stimulation parameters and the achievement of uniform electrical field distribution within complex implant structures. Moreover, the integration of these materials with intricate biological systems necessitates a deeper understanding of endogenous electrical cues and their interplay with other physiological factors. Manufacturing and scalability present further obstacles, with the fabrication of complex 3D scaffolds and nanoscale coatings often proving challenging and costly. Reproducibility and large-scale production remain key concerns. Regulatory hurdles and clinical translation are also significant, mandating the establishment of standardized testing protocols, well-designed clinical trials, and clear regulatory pathways. Finally, the inherent biological complexity and individual patient variability necessitate personalized approaches, demanding more sophisticated in vivo modeling and a thorough understanding of patient-specific responses. Overcoming these multifaceted challenges requires a concerted multidisciplinary effort, fostering collaboration between materials scientists, engineers, biologists, and clinicians to unlock the full potential of electroactive biomaterials in regenerative medicine[20,21].

Future Direction

The future trajectory of electroactive biomaterials in bone regeneration is marked by several pivotal directions, each aimed at enhancing therapeutic efficacy and clinical translatability. A paradigm shift towards smart implants is envisioned, characterized by integrated sensors for real-time monitoring of physiological cues and closed-loop systems that dynamically adjust electrical stimulation based on tissue feedback[19,20,22]. Artificial intelligence will play a crucial role in personalizing implant properties and stimulation protocols, tailoring therapies to individual patient needs. Concurrently, advanced material design and fabrication will focus on developing biodegradable electroactive materials that synchronize with bone regeneration, employing 3D/4D bioprinting for patient-specific scaffolds, integrating nanomaterials to augment electrical and mechanical properties, and exploring self-healing materials for extended implant longevity. A deeper enhanced biological understanding and mechanism elucidation will be pursued, particularly in neural integration, cellular mechanotransduction, vascularization, and immune modulation, to optimize implant-tissue interactions. Robust clinical translation and regulatory pathways are essential, necessitating rigorous preclinical studies in large animal models, well-designed clinical trials, standardized testing protocols, and cost-effective manufacturing processes[23,24,25]. Finally, synergistic therapies and combination approaches will be explored, integrating drug delivery, gene therapy, phototherapy, and stem cell transplantation to achieve comprehensive and enhanced bone regeneration outcomes. This multifaceted approach will pave the way for next-generation electroactive implants, revolutionizing orthopedic and dental therapies.

3. Conclusion:

Electroactive biomaterials represent a cutting-edge paradigm in bone tissue engineering, offering unprecedented control over cellular responses and healing outcomes. The convergence of materials science, bioelectrical engineering, and clinical insights is driving the development of next-generation implants that not only support but actively orchestrate bone regeneration. While significant progress has been made, continued research into smart implants, advanced material design, and robust clinical translation is essential to fully realize the therapeutic potential of electroactive biomaterials, ultimately improving patient outcomes and quality of life.

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