Immunoregulatory Biomaterials for Bone Tissue Engineering: Mechanisms, Design Strategies and Translational Challenges

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Abstract

Bone tissue engineering has progressed from bioinert scaffolds to bioactive and immunoregulatory biomaterials that actively interact with the host immune system. Successful bone regeneration depends not only on osteogenesis but also on the regulation of the immune micro-environment, particularly macrophage polarisation and the balance between pro- and anti-inflammatory responses. This review summarises the interactions between biomaterials and the immune system during bone healing, including host response mechanisms such as protein adsorption, foreign body reaction, and immune cell activation. Key biomaterial properties, such as surface chemistry, topography, mechanical characteristics, and composition, are discussed in relation to their immunomodulatory effects. In addition, current design strategies, including surface modification, ion release, and controlled delivery of bioactive factors, are highlighted. Finally, emerging evaluation approaches and current challenges in clinical translation are briefly discussed, with an outlook towards the development of adaptive biomaterials capable of improving bone regeneration outcomes.

Keywords: bone tissue engineering; osteoimmunology; biomaterials; macrophage polarisation; scaffold design; immune regulation

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1 Introduction

Nanotechnology has emerged as a transformative approach in modern biomedicine, particularly through the development of nanoparticles that enable precise control over material properties at the nanoscale [1]–[5]. These nanostructures exhibit unique physicochemical characteristics, including high surface area-to-volume ratios, tunable surface chemistry, and enhanced bioactivity, which make them highly suitable for biomedical applications [6]–[10]. In the context of bone tissue engineering, nanoparticles play a crucial role in modulating cellular behaviour, promoting osteogenesis, and facilitating targeted delivery of therapeutic agents [11]. More importantly, recent advances highlight their ability to interact with the immune system, opening new avenues for designing immunoregulatory biomaterials that can orchestrate the complex interplay between inflammation and tissue regeneration. This convergence of nanotechnology and immunomodulation provides a promising foundation for developing next-generation strategies aimed at improving bone repair and overcoming current clinical limitations.

The biomaterials used in orthopaedic applications have evolved significantly over the years, starting with bioinert materials, then moving on to the bioactive and biodegradable systems that have been developed to engage in tissue repair. Early materials were chosen primarily based on their mechanical stability and corrosion resistance; however, modern scaffolds are supposed to promote cell adhesion, vascularisation and guided regeneration [12]. Recent studies highlight that contemporary bone tissue engineering integrates osteoconductive matrices, osteoinductive cues, and controlled micro-environmental signalling, rather than relying on passive material [13], [14].

The immune system is no longer considered merely a barrier to implantation; it is now recognised as a primary regulator of tissue regeneration. Recent studies indicate that the nature, duration and spatial organisation of immune signalling significantly influence whether bone healing progresses towards resolution or chronic inflammation [15], [16]. Upon implantation, the material surface is immediately exposed to proteins, immune cells, and stromal components, and these early interactions critically influence subsequent osteogenic outcomes [17].

This review examines the ways in which key biomaterial properties, such as surface chemistry, topography, mechanical stiffness, and composition, regulate immune cell behaviour in bone tissue engineering. It further highlights current design strategies, evaluation methods, translational challenges, and the future directions of smart osteoimmunomodulatory scaffolds [17], [18].

Recent developments in bone tissue engineering emphasise that regenerative success depends not only on the mechanical qualities of the biomaterials, but also on their ability to modulate the host immune response. Bone healing is a coordinated process involving inflammatory, reparative and remodelling phases, in which immune cells, particularly

macrophages, play a central regulatory role [19]. Accordingly, the concept of osteoimmunomodulation has emerged, emphasising that biomaterials should actively interact with the immune system rather than avoid it [20].

Processes that shift macrophage polarisation towards the anti-inflammatory and pro-regenerative (M2) phenotype contribute to enhanced angiogenesis and osteogenesis, instead of the pro-inflammatory (M1) phenotype. Current scaffold design incorporates immunomodulatory strategies, including controlled ion release, cytokine delivery, and surface functionalisation, to direct these cellular responses and create a favourable regenerative micro-environment that promotes tissue regeneration [18]. Despite these advances, challenges remain in achieving precise control over immune responses due to patient-specific variability and complexity of biological systems. Therefore, future biomaterial design should focus on adaptive and responsive systems capable of dynamic regulation to ensure consistent and effective bone regeneration outcomes.

Although there is significant advancement in bone tissue engineering, the current literature has treated biomaterial design and immune response as parallel rather than interrelated processes, which resulted in fragmented understanding of osteoimmunomodulation. This review fills this gap with a mechanistic and integrative model which connects the biomaterial properties with immune regulation and regenerative outcomes. Specifically, it critically evaluates the interplay between physical and biochemical signals, such as surface chemistry, topography, mechanical stiffness, and controlled delivery of bioactive factors in regulating the behaviour of immune cells, with the main emphasis on the dynamics of macrophage polarisation. In addition, the review considers new approaches such as multifunctional scaffold systems and stimuli-responsive biomaterials in the framework of their abilities to provide spatiotemporal control of immune responses. Notably, it also points to the shortcomings of existing evaluation models and translational issues, where the more clinically predictive and adaptive design approaches are needed. Through a combination of these elements, this review will contribute to a more comprehensive and practical insight into immunoregulatory biomaterials to enhance and predict bone regeneration.

2 Bone Regeneration and the Immune System: An Integrated Perspective

Bone regeneration is recognised as an immune-regulated process, not merely a structural or a cellular process. Biomaterials interaction with the host immune system creates a dynamic micro-environment that determines the healing pathway with vital cruciality. After the implantation, early immune response triggers a series of cellular and molecular events which further affects the further tissue regeneration, angiogenesis, and scaffold integration. Here, immune cells are involved not only in inflammatory defence but also play an active role in regulating regenerative signalling pathways by secreting cytokines, communicating between cells and regulating the extracellular matrix. Recent progress in osteoimmunology highlights that effective bone repair is achieved by the precise spatial and temporal control of such immune processes, as

opposed to mere inflammation suppression [15], [21], [22]. The knowledge of the interaction of immune responses and bone healing processes is therefore critical to the rational design of biomaterials that can guide regeneration processes.

Notably, the inflammation to regeneration transition is not a passive transition, but a highly regulated process, entailing a variety of immune cell populations and signalling networks. Any difference in this response, by either long-term pro-inflammatory signalling or lack of resolution, may result in impaired repair, fibrotic encapsulation, or implant failure. In contrast, biomaterials capable of shaping immune responses to a pro-regenerative phenotype have been shown to have better integration and function. New evidence also indicates that immune-mediated control is not just limited to macrophages but also neutrophils, lymphocytes, and osteoimmune interactions that combine to influence the healing environment [23], [24]. These observations reveal the necessity of an in-depth explanation of the role of the immune in various phases of bone repair, as it is explained in the following subsections.

2.1 Stages of Bone Healing and Immune Improvement

The process of bone defect repair is highly coordinated and involves sequential inflammatory, reparative and remodelling phases followed by a series of events in which the immune cells are actively involved in the regulation of tissue repair rather than merely responding to the tissue damage. Recent studies highlight that biomaterial scaffolds are actively involved in the process of regulating these immune stages, thereby guiding the healing process towards successful bone regeneration [19].

Immediately, in response to injury, inflammatory cells remove debris and release cytokines that recruit progenitor cells. This is followed by matrix deposition, angiogenesis and subsequent remodelling of immature tissue into mechanically competent bone [23], [24]. The key to successful repair depends not on the absence of inflammation, but on its timely, proportional and self-limiting inflammation.

2.2 Immune Cell Participation

Neutrophils are the initial responders, and assist in defining the initial inflammatory niche, after which monocytes and macrophages coordinate the alteration from debris clearance to tissue regeneration. M1-type macrophages are linked with pathogen control and phagocytosis, whereas M2-type macrophages promote pro-healing cytokine synthesis, angiogenesis, and matrix remodelling, respectively [14], [15]. Lymphocytes also play a role in maintaining osteoclastogenesis and the inflammatory state and dysregulated T-cell or B-cell activity may exacerbate bone loss and damage repair [25].

2.3 Inflammation–Regeneration Balance

A regulated immune response is important in enhancing osteogenesis and vascularisation. When inflammatory signals persist, the likelihood of osteoclasts activation, fibrotic encapsulation, and slow healing increases; conversely, a sequential

transition to a pro-resolving micro-environment enhances osteoblasts activity and promotes successful scaffold incorporation [17], [24]. The shift of an early inflammatory response to a reparative process is not a spontaneous process but a well-coordinated biological selection (Figure 1). The initial infiltration of M1 macrophages is crucial to the initiation of debris clearance as depicted, but the subsequent transition into M2 type is the major factor in the successful osteogenesis and angiogenesis. During the early inflammatory phase (typically days 1–3), M1 macrophages dominate the defect micro-environment and secrete pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and reactive oxygen species (ROS), which facilitate pathogen clearance, necrotic tissue removal, and recruitment of additional immune cells. Subsequently, during the reparative phase (days 3–7 and beyond), macrophages progressively transition towards the M2 phenotype under the influence of IL-4, IL-10, and TGF-β signalling. M2 macrophages promote extracellular matrix deposition, angiogenesis, osteoprogenitor recruitment, and osteoblastic differentiation through secretion of VEGF, BMP-2, and anti-inflammatory mediators, which supporting successful osseointegration and bone regeneration. The inability to make this switch to polarisation can typically lead to chronic inflammation and fibrotic encapsulation.

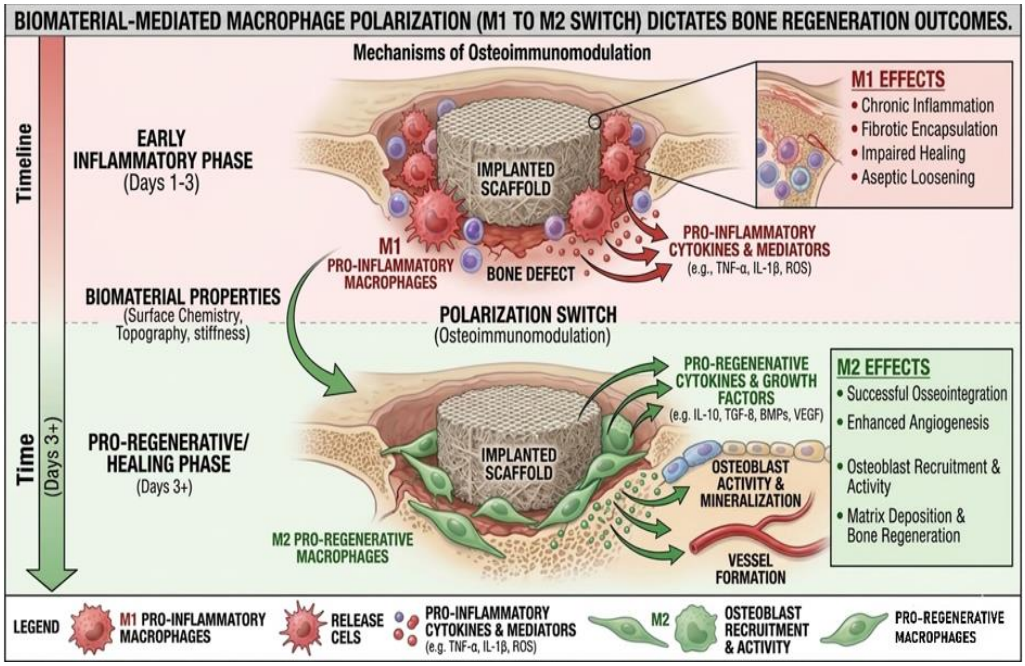

Figure 1: The sequential transition from M1 to M2 macrophages that represents a temporally coordinated immunological process essential to coupling inflammation resolution with angiogenic and osteogenic regeneration

3 Host Immune Response to Implanted Biomaterials

Host immune response to the implanted biomaterials is a very dynamic and sequential process that is critical to determining the success or failure of the tissue integration. When biomaterials encounter biological fluids, a series of events take place immediately after implantation, including protein adsorption and immune cell recruitment, as well as inflammatory signalling pathway activation. The initial events define the biological identity of the implant and determine future cellular reactions [26]. Instead of being a passive response, the host response is a dynamic and active interaction between the material properties and immune responses, which may facilitate a constructive remodelling or cause chronic inflammation and fibrotic encapsulation. Notably, this acute to chronic immune transition is not predetermined but may be affected by the properties of biomaterials, especially by controlling the behaviour of macrophages and inflammatory signalling [16], [17], [27]. The intricacy of the initial host-material interactions and their evolution is therefore critical towards the creation of biomaterials that are capable of directing immune responses towards regenerative results effectively.

3.1 Preliminary Biological Processes: Protein Adsorption and Recruitment

Host response begins within a few seconds of implantation, with the rapid adsorption of plasma proteins to the surface of the biomaterials, which creates a temporary biological identity of the implant. The composition and organisation of this adsorbed sheet of protein impact the complement activation, cell adhesion, and further recruitment of neutrophil and monocyte-derived macrophages [16], [17]. Therefore, surface chemistry and surface energy already dictate early immune interactions before cellular attachment to the scaffold occurs.

3.2 Foreign Body Response: Macrophage Activation and Fibrosis

When acute inflammation persists, the host response may shift to a chronic foreign body reaction (FBR), characterised by persistent macrophage activation, the formation of foreign body giant cells (FBGCs), and fibrotic encapsulation. This response disrupts the integration of the implant with surrounding tissue and limits osteointegration, particularly, in the presence of degradation products or wear debris that persist by reactivating the inflammatory response [28], [29]. Persistent activation of pro-inflammatory macrophages and formation of FBGCs negatively affect osteointegration through several interconnected mechanisms. Elevated secretion of TNF-α, IL-1β, IL-6, and matrix metalloproteinases promote chronic inflammatory signalling and enhances osteoclast differentiation via the RANK/RANKL pathway, resulting in excessive bone resorption around the implant interface. Simultaneously, FBGC-mediated release of degradative enzymes and reactive oxygen intermediates may damage surrounding extracellular matrix components and impair osteoblast viability. Chronic inflammation further stimulates fibroblast activation and collagen-rich fibrous capsule formation, physically isolating the implant from native bone tissue and ultimately compromising vascular infiltration, mechanical fixation, and long-term implant stability.

3.3 Integration Versus Failure of Implants

The survival of clinical outcome of an implant will depend on the possibility of redirecting early immune events towards constructive remodelling. The materials that minimise the excess inflammatory signalling yet allow angiogenesis, recruitment of osteoblasts and renewal of the matrix have higher chances of integrating successfully. Conversely, unresolved inflammation, the unresolved FBR and the imbalance between degradation and tissue formation support loosening, non-union or fibrotic failure [18], [29].

Osteoimmunomodulation has become one of the guiding principles of design of tissue engineering biomaterials, in which the immune system is now considered a vital control over regeneration, rather than an obstacle. Several biomaterials are being developed to take active action against immune cells, especially macrophages to form a pro-healing micro-environment enhancing angiogenesis and osteogenesis [20].

4 Biomaterial Properties Regulating Immune Responses

Being inherent to the immune responses, biomaterial properties are essential to the regulation of the immune responses and therefore the success of the bone regeneration process. Instead of being passive structural supports, the biomaterials are active in controlling cellular behaviour owing to both physicochemical and mechanical signals. Major characteristics such as surface chemistry, topography, stiffness, composition and porosity all influence the initial immune micro-environment by regulating protein adsorption, cell adhesion and signalling pathways. These interactions have a direct impact on the activation of immune cells and in particular macrophage polarisation, which is a key controller of the balance between inflammation and regeneration [16]. An increasing body of evidence shows that the combination of these material properties opens the possibility of coordinated control of immune functions and osteogenic processes and emphasises the significance of designing biomaterials with biological and mechanical functionality [20]. The control of immune behaviour by individual and combined material properties is therefore key to the development of advanced scaffolds able to regulate tissue regeneration, as will be discussed in the following subsections.

4.1 Surface Chemistry and Topography

The initial point of contact between a biomaterial and the host is represented by surface chemistry. Hydroxyl and carboxyl groups enhance wettability and could achieve more favourable protein adsorption profiles, whereas inadequate hydrophobicity may induce denaturation of adsorbed proteins and inflammatory signalling. In addition, surface electric properties influence macrophage polarisation and osteoblast behaviour, so charge modulation is becoming a more significant design strategy [16], [30].

Scaffold mechanical structure provides instructive cues for cellular behaviour. Moderate microscale roughness enhance attachment and early cell signalling, whereas

nanoscale features, for example, nanotubes, nanopillars or grooves, can recapitulate features of the extracellular matrix and regulate morphology and polarisation of macrophages. Regulation of macrophages and osteoclastic-linked signalling at the nanotopographical level has become one of the most promising strategy to enhance osseointegration [31].

4.2 Mechanical Properties and Stiffness

The immune cells are very mechanoresponsive. Substrate stiffness influences cytoskeleton organisation, integrin-mediated signalling and downstream signalling pathway, which regulate inflammatory phenotype and osteogenic crosstalk. Excessively soft matrices may be devoid of structural guidance, whereas overly stiff environments may promote inflammatory activation that cannot be adequately mitigated by surface and biochemical signals [32]. Therefore, mechanical design should be considered not just for load bearing, but also for its role in regulating immune responses.

4.3 Material Composition and Bioactivity

Material composition defines the fundamental biological functioning of a scaffold. Metals based on titanium remain widely used for load-bearing applications and can be further improved through surface modification to enhance osteogenic and antibacterial capabilities [12]. Hydroxyapatite and bioactive glass are bioactive ceramics that are osteoconductive and release bioactive ions, which makes them attractive compound to stimulate bone formation [33]. Polymers are natural and synthetic and can be tailored in terms of degradation rate and processability, whereas biocomposite systems combine the mechanical strength of polymers with the bioactivity of ceramic fillers, offering a more balanced immune-regenerative response [13], [18], [34]–[36].

4.4 Porosity and Structural Architecture

Hierarchical porosity plays a critical role in biomaterial performance by facilitating nutrient transport and vascular infiltration, and increasing the interfacial area for cell-material interactions. Optimised pore size, distribution and interconnectivity are essential to promoting tissue growth and enhancing regenerative outcomes [37]. A summary of key biomaterial properties and their immunoregulatory effects is presented in Table 1. Biomaterials act as active instructors of cellular behaviour through a combination of physiochemical and mechanical signals. Texture-based biomaterials are active instructors of cellular behaviour, which is done through a combination of specific surface topographies, such as nanopillars and optimum matrix stiffness, which directly affect the pro-healing M2 phenotype of the macrophage (Figure 2).

Table 1: Relationship between biomaterial design parameters, immune mechanisms, and bone regeneration outcomes in osteoimmunomodulatory scaffolds

Design parameter/ strategy	Material features/ representative examples	Primary immune mechanism	Key cellular/ molecular response	Regenerative outcome	Translational challenges	Representative references
Surface chemistry modification	Surface electric charge and zeta potential; hydroxyapatite coatings	Modulation of the electric double layer to influence cell-material interactions	Negatively charged surfaces ($−20$ to $−30$ mV) enhance osteoblast activity; positive charges induce pro-inflammatory responses	Enhanced calcium mineralisation and cellular proliferation	Lack of standardised protocols and gaps in mechanistic understanding	[30]
Nano-topographical engineering	Surface nanostructures and focal adhesion-cytoskeleton mediated cues	Regulation of monocyte/ macrophage lineage cell behaviour	Spatiotemporal control of macrophage polarisation and osteoclast differentiation	Establishment of osseointegration and improved implant bear-loading	Optimisation of complex nanostructures for diverse clinical needs	[31]
Mechanical property tuning	Matrix stiffness and substrate rigidity	Mechanobiology-driven modulation of early inflammatory responses	High stiffness increases osteoclast activity; soft substrates favour chondrogenic differentiation	Enhanced bone homeostasis and treatment of large segmental defects	Inconsistent findings owing to variations in stiffness measurement methods	[32]
Bioactive ion incorporation	Therapeutic elements such as zinc (Zn), magnesium (Mg) and silicon (Si)	On-demand release of elements to manipulate the osteoimmune micro-environment	Activation of endogenous biochemical mechanisms for tissue repair	Superior stability and reduced biotic risk compared to growth factors	Controlling release kinetics and biological half-life	[33]
Cytokine and growth factor delivery	IL-10 and IL-4 loaded polymeric microparticles	Induction of pro-regenerative macrophages to dampen chronic inflammation	Sustained MSC osteogenic differentiation in physiologically relevant inflammatory conditions	Reversal of diseases linked to chronic bone loss (eg ONJ)	Safety issues and transient nature of compound release	[38]
Biomimetic scaffold design	3D-printed scaffolds with hierarchical porosity (macro/micro/ nano)	Integration of immunomodulatory factors into native tissue architecture mimics	Coordination of macrophage, osteoclast and osteoblast interactions	Enhanced structural and functional integration with host bone tissue	Manufacturing scalability and establishing functional vascular networks	[37]
Multifunctional integrated systems	AI-driven design and multiscale modelling for patient-specific scaffolds	Synergistic multimodal therapies targeting innate and adaptive immune cells	Active shaping of the pro-regenerative micro-environment	Personalised regenerative therapies for complex defect reconstruction	Regulatory approval and predictive value of preclinical models	[14]
Smart/stimuli-responsive biomaterials	Autonomous systems responsive to pH, temperature or enzymes; optogenetic control	Dynamic interaction with biological cues to regulate macrophage polarisation	Spatiotemporally controlled release of immunomodulatory factors	Active redirection of tissue repair and wound healing outcomes	Long-term biosafety and clinical translation barriers	[17]

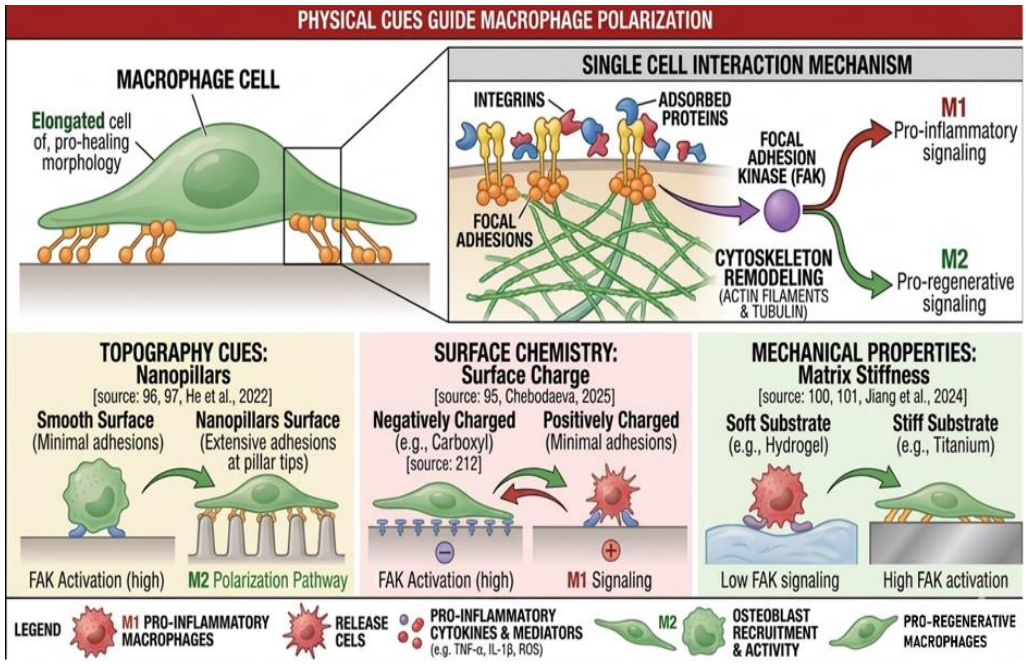

Figure 2: Biomaterial physical cues, including nanotopography, surface charge and stiffness, regulate macrophage cytoskeleton and FAK signalling, which direct polarisation towards pro-inflammatory (M1) or pro-regenerative (M2) phenotypes

5 Immunomodulatory Biomaterial Design Strategies

The design of immunomodulatory biomaterials has become a central focus in bone tissue engineering, moving the focus of tissue engineering to active control of the immune micro-environment instead of passively creating scaffolds. Instead of single-parameter optimisation, recent methods focus on the combinatorial approach to the design that incorporates a combination of various design elements to regulate immune responses and induce tissue regeneration with high precision. Surface modification, nano-topographical engineering, the integration of bioactive ions, and controlled delivery of cytokines and growth factors are all strategies that can regulate the behaviour of immune cells, specifically macrophage polarisation, a key determinant of regenerative outcomes [18]. In addition, the design methods permit the spatiotemporal control of immune responses, which enables biomaterials to replicate the natural inflammatory to regenerative process of bone healing [20].

Importantly, advanced osteoimmunomodulatory biomaterials are increasingly being engineered to emulate the natural temporal sequence of bone healing. In these systems, an initial controlled pro-inflammatory micro-environment supports immune

surveillance and debris clearance, followed by programmed release of anti-inflammatory cytokines, osteogenic ions, or growth factors that promote macrophage polarisation towards the M2 phenotype and initiate tissue repair. Such biomimetic spatiotemporal regulation more closely replicates physiological healing dynamics and may significantly improve angiogenesis, matrix remodelling, and functional osseointegration. Regardless of these progressions, it is difficult to find accurate and predictable immune modulation because of the complexity of biological systems and variability in patients. The evolution of bioadaptive and integrated biomaterial systems would therefore be critical to the further evolution of osteoimmunomodulatory strategies as described in the subsequent subsections.

5.1 Surface Modification Techniques

Surface engineering is a significant strategy for immunomodulation, as the material-tissue interface represents the initial site of the biological interaction. Improved cell adhesion and reduction of excessive inflammatory signalling have been achieved using biofunctional coatings of hydroxyapatite, graphene-based layers, and multifunctional oxide layers. Simultaneously, surface modification of titanium implants can stimulate osteogenic differentiation and minimise microbial risk, which is critical to long-term orthopaedic success [12], [28].

Recent advances in designing biomaterials focus on integrating immunomodulatory functions into biomaterial scaffolds. The current approaches are based on the incorporation of immunomodulatory properties by means of surface modification, controlled ion release, and delivery of bioactive molecules that collectively affect the behaviour of the cells in the process of bone regeneration [18]. As an illustration, surface modification can strengthen protein adsorption and cell-material interactions that influences the macrophage polarisation and healing outcomes. Also, it has been demonstrated that the incorporation of bioactive ions such as calcium, magnesium or silicon can induce osteogenic differentiation while maintaining a balanced inflammatory reaction. Osteoimmunomodulatory-wise, the design strategies should be used to guide the early inflammatory stage to a regenerative stage, alignment with the natural bone healing sequence [19].

In addition, more complex scaffold systems are being designed to deliver cytokines or growth factors in a regulated way, enabling temporally coordinated immune modulation [20]. Despite these advances, the difficulty still lies in ensuring a more accurate control over immune-material interactions owing to the complexity of biological responses, and patient-specific variability.

5.2 Nano-Structuring and Topographical Programming

Increased accuracy in nanoscale architecture can have direct effects on the polarisation of the macrophages and osteogenesis that follows. Optimally sized nanostructured surfaces of titanium, nanotubes, and etched features change the organisation of

cytoskeleton and cytokine release, and tend to prefer a more pro-reparative immune phenotype. These influences are not a mere decor, but a logical approach to programming the early inflammatory niche by designing it physically [18], [31].

5.3 Incorporation of Bioactive ions and Molecules

The other useful approach involves the use of immunoregulatory ions and osteogenic molecules. Examples of elements that can influence macrophage behaviour, promote osteoblast activity and inhibit excessive resorption when released in controlled concentrations include magnesium, zinc, strontium and calcium. The survey of bioactive components indicates that ion-mediated signalling has the ability to integrate immune homeostasis and mineralised tissue formation; this is one of the most appealing paths in the design of multifunctional scaffolds [18], [33].

5.4 Regulated Secretion of Cytokines and Growth Factors

Local delivery systems of cytokines, small molecules and growth factors are also being designed on the basis of scaffolds. Biased induction of macrophages to a pro-healing phenotype by IL-4 or IL-10 release, and an enhancement of tissue integration by osteogenic and angiogenic factor coordination are both possible. Recent studies of controlled delivery in inflammatory micro-environment underpin the idea that spatiotemporal release is required: burst release can be ineffective or even counterproductive, but staged delivery is more physiologically adequate in healing [38].

One of the more sophisticated scaffold design approaches to regulate the local immune micro-environment is the use of immunomodulatory scaffolds including surface functionalisation and controlled ion release. These strategies can be used to direct the immune responses dynamically using biomaterials and to improve regenerative performance [18].

5.5 An Additional Integrative perspective

Another concept that is emerging is that effective osteoimmunomodulatory design needs convergence and not isolation optimisation. Surface chemistry, stiffness, porosity, ion release, and degradation kinetics interact with each other on the same interface and therefore any single change of design variable can alter the behaviour of the others. The rational design of scaffolds is therefore more and more inclined towards integrated platforms, where topography, chemistry, and release behaviour are co-tuned to allow immune resolution and bone formation at the same time [17], [39].

6 Evaluation Methods for Osteoimmunomodulatory Biomaterials

Determining the osteoimmunomodulatory properties of biomaterials must be done on a multidimensional basis going beyond the traditional biocompatibility tests. Conventional assays that only report cytotoxicity or osteogenic ability cannot fully define the intricate interactions between biomaterials and the immune system. Rather,

detailed assessment systems need to combine immunological, cellular and functional tests to determine the effect of biomaterials on the inflammatory process and regeneration. This involves the description of immune cell behaviour, cytokine profiles and their subsequent effects on osteogenesis and tissue integration. There is a growing trend in the field to integrate in vitro with in vivo and more sophisticated microphysiological models to more effectively recapitulate the dynamic and spatiotemporal complexity of the immune micro-environment [18], [40]. A multi-scale and systematic assessment plan is therefore needed to adequately forecast the efficacy of the immunomodulatory biomaterials and to allow their clinical implementation.

Conventional cytotoxicity and proliferation assays alone are insufficient for evaluating immunoregulatory biomaterials because they fail to capture the complexity of immune–biomaterial interactions and inflammatory signalling dynamics. A biomaterial may exhibit acceptable cytocompatibility while simultaneously inducing prolonged macrophage activation, dysregulated cytokine secretion, or fibrotic FBRs that impair long-term regeneration. Evaluation frameworks should therefore integrate immune-specific endpoints including macrophage polarisation profiling, cytokine quantification, inflammasome activation, osteoclastogenesis assessment, and analysis of immune-mediated effects on mesenchymal stem cell osteogenesis.

Standardising immune compatibility alongside cytocompatibility requires establishing reproducible immunological assessment criteria integrated into biomaterial testing pipelines. In addition to ISO-based cytotoxicity testing, future evaluation frameworks should incorporate standardised immune biomarkers, macrophage phenotyping protocols, cytokine-release profiling, and inflammatory index scoring systems under physiologically relevant conditions. Combining these parameters with osteogenic and angiogenic endpoints could provide a more predictive platform for evaluating the regenerative safety and translational potential of osteoimmunomodulatory biomaterials.

6.1 In Vitro Models

Immunomodulatory materials cannot be tested using the traditional cytotoxicity tests. Nowadays, in vitro analysis often involves macrophage polarisation, cytokine analysis, and simultaneous analysis of osteogenic markers. Measurement of markers of the pro-inflammatory and pro-healing macrophage conditions give early indication of whether a material is going to aggravate inflammation or resolve it. Commonly evaluated M1-associated markers include inducible nitric oxide synthase (iNOS), CD86, CCR7, TNF-α and IL-1β, whereas M2 polarisation is typically characterised by expression of CD206, arginase-1 (Arg-1), IL-10, TGF-β, and VEGF. Among these, the combined assessment of CD86/CD206 expression ratios together with cytokine profiling has emerged as one of the most reliable predictors of downstream regenerative performance, particularly with respect to angiogenesis, osteogenic differentiation, and scaffold integration. However, macrophage phenotypes exist along a dynamic continuum, and reliance on single-marker evaluation may oversimplify the complexity of immune-regenerative interactions. The analysis of the secretome is particularly helpful, since the

balance of the cytokines usually forecasts the downstream outcome on mesenchymal stem cells and osteoblasts [14], [18].

6.2 In Vivo Studies

Animal models will still play a vital role in the study of the behavioural dynamics of biomaterials in the prevalent complexity of living tissue. Inflammatory infiltration, angiogenesis, and the formation of new bone are usually evaluated using critical-sized defect models, histology, immunohistochemistry and micro-computed tomography. Such approaches enable researchers to define whether the content in question really promotes the intended switching of inflammatory early stages to beneficial remodelling [23], [37].

6.3 Advanced Platforms (Organ-on-Chip and 3D Models)

In an effort to enhance the importance of human relevance, co-culture systems and microphysiological models are increasingly being embraced in the field. Compared to conventional monoculture systems, macrophage–mesenchymal stem cell (MSC) co-culture models provide substantially greater predictive value because they better reproduce the bidirectional paracrine signalling and immunoregulatory crosstalk that occur during bone healing. These systems enable simultaneous evaluation of inflammatory activation, macrophage polarisation, MSC recruitment, and osteogenic differentiation within a shared micro-environment. Consequently, co-culture platforms offer improved translational relevance for assessing how biomaterials influence immune-mediated regeneration and are increasingly considered essential tools for preclinical osteoimmunomodulatory evaluation. Important paracrine crosstalk is lost in monocultures, whereas in macrophage-osteoblast or macrophage-stem-cell co-cultures, important interactions can be captured, and in immunocompetent organ-on-chip systems, flow, mechanical cues, and multicellular interaction can be better approximated. The immune-competent chip platforms and orthopaedic co-culture models are therefore effective in between cell culture and animal experiments [40]–[42].

7 Recent Problems and Limitations

Although immunomodulatory biomaterials design has gone a long way, there are still numerous challenges that need to be overcome to effectively translate the materials in clinical settings. The main limitation is due to the complex and dynamic interactions between the immune system and biomaterials where even minor changes in the material properties may cause unpredictable immune reactions and uneven regenerative results [43]. The host immune response is very complex and contextual and it is a matter of competing interaction of immune cells, tissue cells and external forces such as bacterial contamination which can upset the balance between inflammation and regeneration [44].

Numerous biomaterial systems show encouraging outcomes in a controlled laboratory setting but cannot be reproduced in the same conditions in clinical settings because of the distinctions in immune responses and long-term biology [18]. These challenges highlight a critical gap between experimental success and clinical applicability, emphasising the need for more robust, predictive and patient-adaptive design strategies.

7.1 Patient-Specific Variability

One of the biggest impediments to clinical translation is the heterogeneity of the human immune system. Inflammatory tone and healing capacity are also dependent on age, sex, nutrition, chronic disease, and medication history and such that a scaffold that is successful in a uniform animal model might act differently in the complex patient populations. The variability of the baseline immunity has become one of the central causes of inconsistent results of regenerative therapies in different patients [16], [45].

7.2 Chronic Inflammation and Long-Term Implant Stability

Although the initial implantation seems to be working, wear particles, corrosion products or an incompatible rate of degradation may impair long-term performance. The continued low-grade inflammation may restart osteolysis, facilitate fibrotic encapsulation, and eventually cause aseptic loosening or mechanical failure. Regulating the long-term foreign body response is therefore equally significant to that of regulating the acute response right after surgery [28], [29].

7.3 Laboratory to Clinical Practice Translation

Cost, regulatory complexity and reproducibility of manufacturing remain a hindrance to translation. Multifunctional scaffolds with bioactive ions, coating, and drug-delivery capabilities can be highly preclinical, but are less readily reproducible at industrial levels and sometimes undergo greater regulatory scrutiny. The economic feasibility is also important, particularly in the cases when advanced biologics or nanocarriers are needed to be effective [37], [39].

Although remarkable progress has been made in the design of immunomodulatory scaffolds, there are still problems with successful clinical translation. The immune responses variability, complexity of scaffold fabrication, and lack of long-term in vivo validation still prevent widespread clinical adoption [18].

8 Future Prospectives and Emerging Trends

In osteoimmunomodulatory biomaterials, future trends are predicted to shift away to dynamic scaffold design and multifunctional systems that are able to effectively respond to the host immune environment. To control immune reactions in spatiotemporal fashion, smart and stimuli-responsive biomaterials are being designed to recapitulate the natural development of bone healing. Simultaneously, novel fabrication technologies and data-driven design strategies allow controlling the scaffold

architecture and bioactive signalling with high precision. Enhancing translational predictability is also a priority, and human-relevant models such as organ-on-chip models increase the accuracy of preclinical testing [40]. The development of knowledge on the foreign body response underscores the significance of long-term immune regulation in the integration of the implantation [20], [46].

8.1 Dynamic and Stimulus Response Systems

It is probable that in the future bone tissue engineering will not be based on simply stationary scaffolds but rather materials that dynamically react to local biological signals. The response to pH, inflammatory mediators, oxidative stress or mechanical variations may allow release of immunomodulators only on demand, eliminating off-target actions and preserving regenerative properties in smart biomaterials. This idea is an extension of the passive implants to adaptive therapeutic platforms [14], [39]. The future of bone tissue engineering will be the creation of smart therapeutic platforms that dynamically react to the local environment (Figure 3). Instead of static released, such systems are based on biological triggers, such as localised pH drops or enzymatic activity, to trigger the on-demand release of bioactive ions and growth factors. Such spatiotemporal control enables the scaffold to mimic the natural bone healing programme, whereby regenerative signals are only released when the biological niche is prepared to respond.

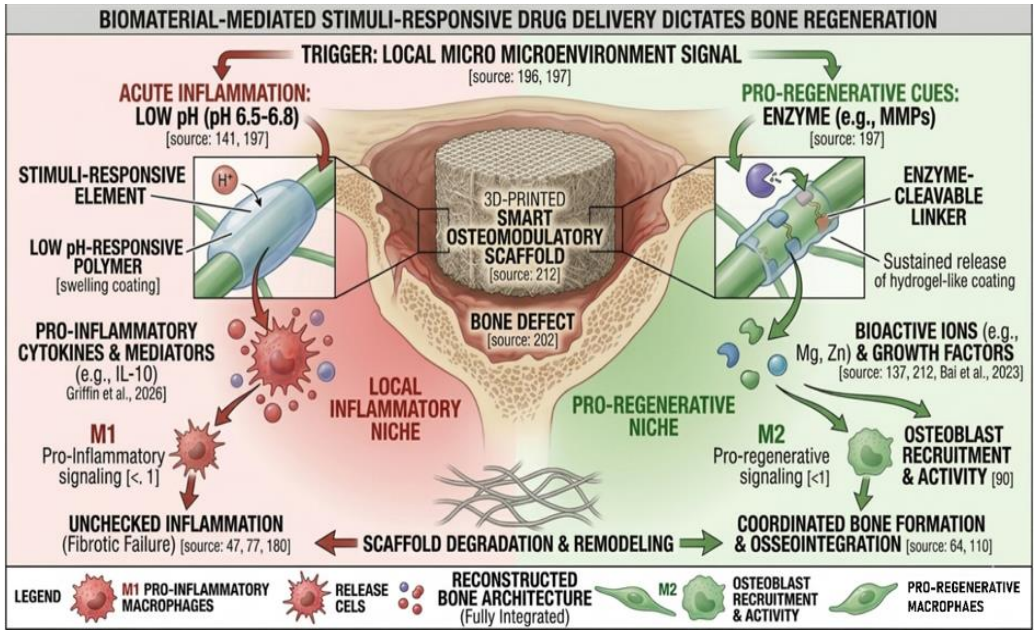

Figure 3: Smart osteoimmunomodulatory scaffolds that respond to local stimuli such as low pH and enzymatic activity to trigger controlled release of anti-inflammatory agents, bioactive ions and growth factors, promoting coordinated bone regeneration and osseointegration

8.2 High Technology Fabrication and Design

New fabrication techniques such as 3D and 4D printing enable the progressively controlled pore architecture, gradient placement and time-resolving conduct. The tools can be used to rationalise scaffold mechanics, degradation and signalling with disease-specific defects. Meanwhile, data-driven design methods are emerging to aid in forecasting the interplay between topography, stiffness and chemistry to determine cell-material interactions, which could be used to optimise osteoimmunomodulatory scaffolds more quickly [37], [39].

8.3 Towards Clinically Predictive Testing

The other significant future trend is the creation of more realistic evaluation systems based on human biology. Immune models that are humanised chip-based systems and integrated co-culture platforms have the potential to decrease the gap between the good laboratory results and the depressed clinical results. These tools should be made to prioritise candidate biomaterials to produce long-term and clinically beneficial immune responses, rather than just osteogenic potential as they mature [40], [41].

9 Conclusion

The bone tissue engineering paradigm has changed, and it is currently focused on reducing host interaction to actively instruct the immune micro-environment. The existing evidence demonstrates that scaffold chemistry, topography, stiffness, composition, and delivery behaviour all play an important role in the regenerative or destructive response of the immune system. Despite the existing difficulties in translation, osteoimmunological understanding of bone regeneration combined with the development of novel biomaterials is a promising avenue to more predictable, personalised, and effective bone regeneration.

10 Author Contributions

Muhammad Rizwan Khan: conceptualisation of the review theme; literature search and data mining; and drafting of the initial manuscript. Bushra Ashiq: conceptualisation of the review theme, collection and classification of recent literature; and design of the mechanistic illustrations. Muzammil Sattar and Muhammad Naeem Bajwa: critical revision of the manuscript for intellectual content; and overall validation of the comparative analyses of various metal oxide systems. All authors have read and approved the final version of the manuscript for submission.

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