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Review

Mechanically Dynamic and Immuno-Instructive Biomaterials: Converging Strategies to Direct Cell Fate in Regenerative Microenvironments

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Abstract

Tissue regeneration is influenced by the dynamic interactions between cells and the extracellular matrix (ECM), in which the repair outcomes are collectively determined by the evolving mechanical properties and strictly regulated immune responses. Conventional biomaterials, which are typically immunologically inert and mechanically static, are unable to replicate the adaptive and inflammatory-responsive characteristics of native regenerative microenvironments. Adaptive hydrogel networks, tuneable stiffness, viscoelasticity, stress relaxation, and mechanically dynamic biomaterials have been shown to regulate the fate of stem cells through mechanotransduction pathways that involve Yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) signalling, cytoskeletal remodelling, and integrins. At the same time, immuno-instructive biomaterials have become important modulators of interactions between biomaterials and immune cells. They affect the functional plasticity of macrophages beyond the traditional M1/M2 framework, guide cytokine profiles, and shape tissue-specific responses like osteoimmunological regulation. Increasing evidence suggests that mechanical cues and inflammatory processes are mechanistically coupled during the healing process, with matrix remodelling influencing immune behaviour and vice versa. A promising approach to the development of ECM-mimetic scaffolds that can orchestrate coordinated tissue repair is provided by convergent design strategies that incorporate immune modulation with mechanical adaptability. The consideration of host responses, degradation kinetics, and translational challenges is still necessary for clinical implementation. Integrating immuno-instructive and mechanically dynamic principles is a biologically informed approach to regulating cell fate in regenerative microenvironments.

Keywords: Adaptive hydrogel networks, immuno-instructive biomaterials, mechanotransduction pathways, mechanical-immune coupling, ECM-mimetic scaffolds, regenerative medicine.

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Introduction

The viability of tissue regeneration is contingent upon the sophisticated coordination of interactions between cells and the extracellular matrix (ECM). In the past, regenerative biomaterials were developed to deliver bioactive molecules, fill defects, or provide structural support [1]. Nevertheless, it is now widely recognized that regeneration is not solely controlled by biochemical signals; rather, it is the result of the dynamic interplay between cellular mechanotransduction pathways, immune responses, and mechanical cues [2]. Through cytoskeletal contractility, nuclear mechanosensing, and integrin-mediated adhesions, cells continuously monitor their physical environment, transforming matrix-derived forces into transcriptional programs which regulate proliferation, migration, as well as lineage specification [3]. The significance of cell–material interactions is particularly apparent in musculoskeletal tissues, such as bone and cartilage. A precise equilibrium is necessary for bone regeneration, which necessitates the coordination of immune cells, vascularization, osteoclast-driven remodelling, and matrix deposition mediated by osteoblasts [4]. Additionally, cartilage repair necessitates the preservation of the chondrocyte phenotype within a mechanically specialized and avascular microen-

vironment. These intricate systems are disrupted by injury, which affects immune homeostasis and mechanical integrity. Consequently, biomaterials that are intended for the repair of bone and cartilage must surpass the confines of static mechanical matching and instead replicate the dynamic microenvironment that is an attribute of natural healing [5].

Their mechanical dynamism is one of the distinguishing characteristics of native regenerative niches. For instance, the initial hematoma as well as soft callus is mechanically compliant during fracture healing, which facilitates vascular ingrowth and cell infiltration. The matrix stiffens as healing progresses, facilitating osteogenic maturation through mineralization and collagen deposition [6]. In the context of cartilage repair, transient soft matrices may facilitate chondrogenic differentiation, while excessive rigidity can promote hypertrophy or fibrotic responses. These temporal mechanical transitions have a significant impact on the judgments regarding the fate of stem cells. Even though inert biomaterials are calibrated to match the initial tissue stiffness, they are unable to replicate these dynamic variations. At the same time, the immune system coordinates tissue repair [7].

Neutrophils and macrophages are recruited during early inflammatory responses, which facilitate the clearance of debris and the release of cytokines that affect the behaviour of progenitor cells. As part of bone healing, macrophages modulate osteogenesis by coupling with osteoclast activity and using paracrine signalling. Dysregulated inflammation is a contributing factor to the degradation of the matrix and the progression of osteoarthritis in cartilage injury [8]. Consequently, immune modulation is not limited to the peripheral but rather is essential for the efficacy of regenerative processes. It is crucial to note that the phenotype of immune cells is influenced by mechanical cues, which establishes a bidirectional feedback cycle between inflammation and matrix mechanics [9].

These insights have facilitated the development of biomaterials that are both immuno-instructive and mechanically dynamic, which are engineered systems that can manipulate immune responses while concurrently adapting their physical properties. While fostering a pro-regenerative immune environment, these materials are designed to replicate the changing mechanical landscape of regenerating tissues. This method has the potential to improve osteogenesis, preserve the chondrogenic phenotype, and decrease fibrotic encapsulation in bone and cartilage applications [10,11]. Despite significant developments in biomaterial design, current techniques frequently focus mechanical qualities or immune regulation separately, ignoring their inherent interconnectedness within dynamic regenerative microenvironments [12,13]. This fragmented approach restricts our capacity to properly capture the complexities of native tissue healing, where structural, mechanical, and immunological stimuli are tightly connected and develop as time progresses. As a result, a complete framework integrating material structure, biomechanical behaviour, and immunological training is important [14, 15]. This review integrates these characteristics to show how mechanically dynamic and immuno-instructive biomaterials can rationally regulate cell destiny through coordinated physicochemical and biological signals. This work bridges mechanobiology and immunoengineering, providing a conceptual and design-oriented roadmap for designing next-generation regenerative systems, particularly for complex tissues like bone and cartilage. This study also highlights knowledge gaps and opportunities, such as spatiotemporally adaptive materials, patient-specific design methodologies, and enhanced *in vitro–in vivo* translation models. These findings should help researchers design smart, responsive biomaterials that dynamically interact with developing microenvironments to improve precision regenerative medicine and clinical outcomes.

Native Regenerative Microenvironments

Tissue regeneration is not a process that occurs in isolation; rather, it occurs within a microenvironment that is highly dynamic and consists of ECM, resident and infiltrating cells, soluble signalling molecules, and mechanical forces. This microenvironment is particularly intricate in musculoskeletal tissues, such as bone and cartilage, because of the tightly regulated immune–mechanical coupling and load-bearing demands. Mechanical properties and inflammatory signalling endure rapid and coordinated changes that collectively influence matrix remodelling, differentiation, and cell recruitment following injury. The rational design of biomaterials that are intended to replicate or steer these processes is contingent upon an understanding of these native regenerative dynamics [16,17].

The structural organization of the material influences its biomechanical behaviour and, subsequently, the cellular microenvironment; this is an important but frequently neglected factor in biomaterial performance. Important mechanical characteristics including rigidity, viscoelasticity, permeability, and stress distribution are determined by the material's structure, which includes factors like porosity, fiber orientation, surface roughness, hierarchical architecture, and crosslinking density. As an example, networks that are densely packed and crosslinked tend to be more rigid and have less stress relaxation, whereas matrices that are porous or just lightly crosslinked allow for better fluid movement, cell infiltration, and remodelling of the matrix. These structural elements play an essential role in cell sensing by regulating local mechanical heterogeneity and defining bulk mechanical characteristics [18]. Mechanotransduction pathways, nutrition transport, immune cell infiltration, and spatial cytokine gradients are all affected by the biophysical milieu that cells encounter, which is in turn shaped by the structural design of biomaterials. Surface characteristics at the nanoscale control protein adsorption

and the activation of immune cells; anisotropic or aligned fibrous structures, for instance, can guide cell movement and direction. An analogous relationship exists between pore size and interconnectedness, which govern oxygen delivery and waste disposal; in turn, these factors impact stem cell fate and inflammatory responses. Engineered design, biomechanical cues, and the spatiotemporal evolution of the regenerative milieu are all interconnected via material structure, which serves as a foundational regulator. Therefore, it is imperative to possess a thorough comprehension of the structure–property–function relationship in order to develop biomaterials that can precisely and dynamically direct both cellular and immune responses [19,20].

Mechanical Characteristics of Healthy Versus Injured Tissues

The mechanical architectures of healthy bone and cartilage are highly regulated yet distinct, and they are essential for their function and cellular homeostasis [21]. Bone is a mineralized composite tissue that is hierarchically structured and composed of collagen fibrils that are reinforced with hydroxyapatite crystals. It is known for its high rigidity, strength, and resistance to mechanical loading [22]. Its multiscale organization, which encompasses trabecular and cortical macrostructures, trabecular mineralized collagen, and nanoscale mineralized collagen, facilitates continuous adaptation through remodelling and efficient load transfer [23]. Conversely, articular cartilage is a viscoelastic tissue that is highly hydrated and contains proteoglycans and type II collagen. It is engineered to endure repetitive compressive forces while ensuring that the joint surfaces are low friction. Its mechanical behaviour is distinguished by elastic stiffness and time-dependent properties, including fluid pressurization and stress relaxation, which are essential for the study of chondrocyte mechanobiology [24]. The mechanical microenvironment of both tissues endures significant changes after injury. Initially compliant hematomas are formed in bone fractures, establishing a malleable and permissive environment for the recruitment of mesenchymal stem cells (MSCs) and the infiltration of immune cells [25]. In a temporally regulated manner, this environment gradually transitions into a fibrocartilaginous callus and subsequently mineralized bone, resulting in a gradual stiffening that directs chondrogenic and osteogenic differentiation [26]. The depletion of proteoglycans and the disruption of collagen architecture in cartilage defects result in a reduction in compressive rigidity and an impairment in viscoelastic load distribution. This leads to abnormal mechanotransduction and an increased susceptibility to degeneration [27]. In contrast to bone, cartilage is characterized by its lack of intrinsic vascularization and robust remodelling capacity, which renders the restoration of its precise mechanical environment particularly difficult. Therefore, the regeneration of both bone and cartilage takes place within mechanical landscapes that are in a state of dynamic evolution. The cellular responses and overall healing outcomes are significantly influenced by changes in matrix organization, viscoelasticity, and rigidity [28]. These intrinsic mechanical qualities are inherently linked to the hierarchical structural organization of tissues, ranging from nanoscale collagen arrangement to nanoscale architecture. Mimicking such multiscale structural properties in biomaterials is therefore critical, as even minor differences in scaffold architecture can drastically influence local stiffness, stress distribution, and, ultimately, the cellular microenvironment.

Role of Immune Response in Tissue Repair

In addition to serving as a defence mechanism, the immune response is a critical regulator of tissue repair, actively coordinating regeneration in both bone and cartilage. The innate immune system initiates an inflammatory cascade immediately after injury, which can be defined by the invasion of neutrophils along with monocyte-derived macrophages to the defect site [29]. These early immune cells eliminate debris and pathogens while simultaneously discharging both cytokines and chemokines which mobilize MSCs and promote angiogenesis. This initial inflammatory phase is crucial for the formation of calluses in bone healing, as macrophages secrete growth factors that facilitate osteoblast differentiation and vascular integration, thereby coordinating the transition from inflammation to regeneration [30]. In addition, osteoclasts, which are derived from the monocyte/macrophage lineage, are involved in remodelling, which promises the appropriate connection between resorption and the formation of new bone. However, osteogenesis can be impaired and fibrotic tissue formation or delayed union can result from dysregulated or prolonged inflammation [31]. The avascular and immune-privileged nature of cartilage renders immune regulation even more delicate during the repair process. Matrix-degrading enzymes are stimulated, anabolic activity of chondrocytes is suppressed, and progressive cartilage degeneration and osteoarthritic alterations are facilitated by elevated pro-inflammatory cytokines, including IL-1β and TNF-α. The resolution of inflammation is essential for the preservation of ECM integrity and the maintenance of the chondrocyte phenotype, as cartilage lacks a robust intrinsic remodelling capacity, in contrast to bone [32]. Consequently, the significance of developing biomaterials that can regulate immune responses in a chronologically and spatially coordinated manner is made apparent by the fact that effective tissue regeneration in both bone and cartilage is contingent upon a tightly controlled temporal growth from an early inflammatory phase to a pro-regenerative environment [33].

Coupling Between Mechanics and Inflammation

Recent research has proved a dual connection between immune behaviour and mechanical stimuli. The morphology, cytoskeletal tension, and cytokine secretion parame-

ters of macrophages are directly influenced by matrix rigidity, viscoelasticity, and topography (Fig. 1) [34,35]. The physicomechanical analysis using atomic force microscopy further confirmed graded stiffness increases from healthy livers through steatosis, steatohepatitis, and fibrosis. This was further validated in a mouse model wherein rheometry demonstrated corresponding increases in Young's modulus and storage modulus (G′), which correlated with histological scores, lipid area, matrix proteins (e.g., MMP2, collagen I), serum injury markers (AST/ALT), and cytokines (IL-6, TNF-α, IL-1β). In addition, pro-inflammatory signalling pathways can be facilitated by stiffer substrates due to increased cytoskeletal contractility, whereas pro-regenerative phenotypes may be promoted by compliant or stress-relaxing matrices. In contrast, inflammation alters the mechanical characteristics of the tissue [35]. Fibrosis or excessive crosslinking can result in abnormal stiffening, while cytokine-mediated matrix degradation reduces rigidity. In bone, osteoclast activity is regulated by inflammatory mediators, which results in alterations to structural integrity [36]. The compressive resilience of cartilage is reduced as a result of the disruption of proteoglycan content by catabolic signalling. This feedback loop is a dynamic example of how immunity and mechanics cannot be viewed in isolation. Rather, they serve as regeneration regulators that are integrated. Mechanical stabilization that is appropriate for bone facilitates the resolution of inflammation and the progression toward mineralization. In cartilage, matrix restoration is facilitated by moderated inflammatory signalling and controlled mechanical loading [37,38].

In addition to mechanical inputs influencing immune behaviour, immunological responses actively remodel and redefine the mechanical properties of the microenvironment, resulting in a dynamic and reciprocal feedback loop. Activated immune cells, notably macrophages and neutrophils, secrete matrix-degrading enzymes called matrix metalloproteinases (MMPs), which cleave ECM components, resulting in reduced matrix stiffness and altered viscoelastic characteristics. In contrast, chronic or dysregulated inflammation can promote fibrotic remodelling, which is characterized by excessive collagen deposition and crosslinking, resulting in pathological tissue stiffening [39]. Immune-regulated osteoclast activity in bone promotes matrix resorption, which directly influences structural integrity and mechanical strength during both healing and disease progression. Pro-inflammatory cytokines like IL-1β and TNF-α in cartilage cause degradation of proteoglycans and collagen networks, reducing compressive resistance and changing load distribution. These immune-driven changes in matrix composition and architecture dynamically modify the biomechanical landscape, which then influences mechanotransduction pathways and cell fate decisions. As a result, immunological activity should be considered not only as a biological regulator, but also as a significant factor of the altering mechanical microenvironment during tissue regeneration. This bidirectional interplay highlights that mechanics and immunity are co-evolving regulators of regeneration rather than independent factors [40].

Implications for Biomaterial Design

The dynamic interplay between immune regulation and mechanics in the repair of native cartilage and tendons offers essential guidance for the development of next-generation biomaterials. Traditional scaffolds that are designed to match the static rigidity of target tissues are inadequate for the replication of the dynamic regenerative microenvironment [41]. In contrast, biomaterials must be designed to adapt temporally, aligning with the progressive mechanical transitions that are observed during the healing process. For instance, the maintenance of a viscoelastic, hydrated microenvironment during cartilage regeneration or the transition from a responsive inflammatory region to a mechanically stable, matrix-rich environment during bone repair [42].

The ability to regulate immune responses in a controlled manner is equally significant. To prevent fibrosis or protracted degeneration, materials should facilitate the timely resolution of pro-regenerative signalling while supporting the early inflammatory phase, which is essential for debris clearance and cell recruitment [43]. Macrophage phenotype, cytokine secretion, and progenitor cell differentiation must be strategically influenced by the strategic integration of surface chemistry, topography, degradation kinetics, and mechanical behaviour. For bone applications, scaffolds may necessitate progressive stiffening, osteoconductive cues, and support for vascularization [44]. Conversely, cartilage-cantered systems must protect compressive resilience, mitigate persistent inflammation, and maintain chondrocyte phenotype stability. To prevent chronic foreign body responses, degradation by-products must be non-immunogenic and synchronized with tissue remodelling rates [45,46].

Mechanically Dynamic Biomaterials

An engineered system, mechanically dynamic biomaterials are intended to replicate the changing physical characteristics of native regenerative microenvironments. In contrast to traditional static scaffolds, these materials feature adaptive crosslinking networks, cell-responsive degradation mechanisms, time-dependent viscoelastic behaviour, and tuneable stiffness [13]. The capacity of a biomaterial to send controlled and dynamic mechanical signals is crucial for the regulation of stem cell fate, matrix deposition, and long-term functional integration in musculoskeletal tissues, such as bone and cartilage, where healing is significantly influenced by mechanical cues. Mechanically dynamic biomaterials actively direct cellular behaviour by regulating cytoskeletal tension, focal adhesion maturation, as well as nuclear mechanotransduction pathways, as opposed to merely providing structural support [47].

Stiffness and Stem Cell Fate

A mechanical regulator of stem cell behaviour that has been extensively investigated is matrix stiffness. The actin cytoskeleton is connected to extracellular ligands by integrin-mediated adhesions, which are how cells detect substrate elasticity. Cytoskeletal contractility, focal adhesion assembly, and intracellular signalling cascades are all influenced by changes in stiffness, which ultimately modulate gene expression [48]. By promoting cytoskeletal tension and activating osteogenic transcription factors, relatively rigid matrices facilitate osteogenic differentiation of MSCs in bone regeneration. The nuclear localization of mechanosensitive regulators is facilitated by the increased substrate rigidity, which results in the upregulation of osteogenic markers and mineral deposition [49]. However, the temporal regulation of stiffness is crucial, as excessive stiffness during the early phases may impede cell infiltration and vascularization. Conversely, cartilage regeneration frequently capitalizes on softer matrices that more closely resemble complies with and hydrated nature of native cartilage [50]. Chondrogenic differentiation is facilitated by substrates with moderate elasticity, while hypertrophic or fibrotic responses are minimized. Furthermore, optimal rigidity is not universal; rather, it is tissue-specific and temporally regulated. Biomaterials that are mechanically dynamic and enable the progressive modulation of rigidity during the healing process may more accurately replicate the physiological repair processes across both bone and cartilage [51].

Viscoelasticity and Stress Relaxation

Native tissues demonstrate substantial viscoelastic behaviour, which is defined by tension relaxation, creep, and time-dependent deformation, even though elastic modulus offers valuable information regarding matrix stiffness. By dissipating applied forces over time, viscoelastic materials enable cells to remodel their surrounding matrix, thereby influencing proliferation, differentiation, and propagation [52]. Although their initial rigidity is relatively modest, stress-relaxing hydrogels have been demonstrated to improve osteogenic differentiation in bone tissue engineering. Cytoskeletal reorganization and matrix deposition are facilitated by rapid stress relaxation, which supports mineralization. This implies that time-dependent mechanical properties may be as influential as static rigidity in guiding osteogenesis [53]. Similarly, viscoelastic scaffolds are more effective in emulating the load-bearing behaviour of native cartilage during cartilage regeneration, thereby preserving compressive resilience and fluid pressurization. These characteristics are indispensable for the preservation of the chondrocyte phenotype and the stimulation of glycosaminoglycan synthesis [54]. Cellular remodelling may be restricted, and long-term functional outcomes may be compromised by materials that do not provide adequate tension relaxation. Consequently, it is imperative to develop biomaterials with viscoelastic responses that can be adjusted to replicate musculoskeletal microenvironments [55].

Dynamic and Adaptive Hydrogels

Dynamic and adaptive hydrogels are a smart category of biomaterials that are mechanically responsive and are intended to replicate the continuously changing ECM that is observed during tissue repair [56]. These systems, in contrast to permanently crosslinked hydrogels with fixed stiffness, consist of reversible physical interactions, dynamic covalent bonds, supramolecular assemblies, or enzyme-sensitive linkages that enable the temporal modulation of mechanical properties, degradation, and network architecture. This adaptability is especially pertinent in the context of musculoskeletal regeneration, which involves the execution of sequential mechanical transitions to facilitate healing [57]. In the process of bone repair, the microenvironment undergoes a transition from a compliant inflammatory niche to a progressively stiff, mineralized matrix. Hydrogels that are capable of gradual stiffening or cell-mediated remodelling can replicate this transition, thereby support early cell infiltration and vascularization while later promoting osteogenic maturation through strengthened cytoskeletal tension and mechanotransduction [58]. In contrast, the maintenance of a chondrocyte phenotype and the prevention of hypertrophic differentiation necessitate the preservation of a moderately compliant, viscoelastic, and hydrated environment for cartilage regeneration [59]. Dynamic hydrogels, which possess reversible crosslinks and rapid stress relaxation, enable cellular remodelling while maintaining compressive resilience, thereby more accurately replicating the mechanics of native cartilage. Furthermore, the synchronization of scaffold resorption with new matrix deposition is facilitated by enzyme-responsive degradation, which reduces chronic inflammation and facilitates long-term integration [60]. Adaptive hydrogels function as active regulators of the regenerative microenvironment in both bone and cartilage repair by facilitating reciprocal interactions between cells and their mechanical environs, thereby transcending passive structural support [61].

Mechanotransduction Pathways (Integrins, YAP/TAZ, Cytoskeleton)

Mechanotransduction is the process by which cells detect mechanical signals from their immediate surroundings and turn them into biochemical signals that control gene expression, phenotype, and function. This mechanism is essential for the regeneration of bone and cartilage, as both tissues are intensely mechanosensitive and loadbearing [62]. Cytoskeletal tension and receptor-mediated adhesion are the mechanisms by which cells actively investigate their environment, adjusting their behaviour in accordance with matrix stiffness, viscoelasticity, and topography, they do not respond to mechanical properties passively. It is im-

perative to comprehend these pathways to develop biomaterials that are mechanically dynamic and capable of directing tissue-specific regeneration [63]. Integrins, transmembrane receptors that connect ECM ligands which include proteins such as collagen, fibronectin, or laminin to the intracellular actin cytoskeleton by means of focal adhesion complexes, are at the heart of mechanosensing. Integrins cluster and recruit adaptor proteins, such as talin, vinculin, and focal adhesion kinase (FAK), upon binding to matrix ligands, thereby establishing mechanosensitive signalling centres [64]. The size and maturation of focal adhesions are directly influenced by the rigidity of the substrate. Stiffer matrices promote stronger integrin clustering and increase cytoskeletal tension, whereas softer matrices limit focal adhesion assembly [65]. Enhanced integrin engagement on stiffer substrates in bone regeneration promotes osteogenic differentiation by activating downstream signalling pathways, including FAK–ERK and RhoA/ROCK. However, in cartilage, the necessity of a balanced mechanical presentation is underscored by the potential for excessive integrin-mediated tension to disrupt the chondrocyte phenotype and promote dedifferentiation [66]. The primary intracellular force-transmitting structure is the actin cytoskeleton. RhoA/ROCK signalling is activated by mechanical stimuli transmitted through integrins, which results in an increase in actomyosin contractility and the generation of intracellular tension. In addition to regulating cell dispersion and morphology, this cytoskeletal tension also affects nuclear mechanics. In osteogenic environments, the expression of osteoblastic genes and mineralization are facilitated by the formation of more actin stress fibres [67]. Conversely, the preservation of cartilage-specific markers and the prevention of fibrocartilaginous transition are contingent upon the maintenance of a rounded chondrocyte morphology with controlled cytoskeletal tension in cartilage [68].

Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are key regulators of mechanical signal integration. These proteins are mechanosensitive and transit between the nucleus and cytoplasm in response to matrix stiffness and cytoskeletal tension. Under high mechanical loading or on stiff substrates, YAP/TAZ translocate to the nucleus, where they engage with transcription factors to modulate genes associated with matrix production, differentiation, and proliferation. Osteogenic commitment as well as matrix mineralization is facilitated by the nuclear localization of YAP/TAZ in bone regeneration. However, the temporal and tissue-specific modulation of these pathways is essential, as sustained YAP/TAZ activation may induce hypertrophy or catabolic responses in cartilage repair [69].

In addition to YAP/TAZ, mechanical forces also affect epigenetic regulation, chromatin organization, and nuclear deformation. The Linker of Nucleoskeleton and Cytoskeleton (LINC) complex facilitates the direct transmission of mechanical stress to the nuclear envelope by connecting the cytoskeleton to the nucleus. Chromatin accessibility and transcriptional activity can be influenced by changes in nuclear morphology, which serves as a mechanism for long-term ”mechanical memory.” In bone, epigenetic modifications are induced by mechanical loading, which enhances osteogenic gene expression. Conversely, in cartilage, aberrant mechanical stress may initiate persistent inflammatory as well as degradative gene programs [70,71].

Shape-Morphing and 4D Biomaterials in Regeneration

Recent breakthroughs in 4D biomaterials have presented a transformative paradigm in which material structure and function vary over time in response to external or endogenous stimuli, allowing for dynamic control of the cellular microenvironment. Unlike static scaffolds, 4D systems use time as a functional dimension to enable planned shape modification, mechanical adaption, and microenvironmental remodelling. These materials are often designed using spatially heterogeneous architectures, gradient crosslinking, or multi-material printing to provide differential swelling, degradation, or stress distribution, resulting in controlled deformation [72]. Shape-morphing in 4D biomaterials can be divided into two categories: externally induced and cell-mediated (endogenous). External stimuli, including as temperature, light, magnetic fields, and chemical gradients, have long been employed to cause predictable transformations like bending, folding, and twisting. These techniques provide accurate temporal control but may lack full physiological significance due to their reliance on external actuation. In contrast, emerging systems use cell contractile forces (CCFs) as intrinsic shape transformation drivers, providing a more biomimetic approach to tissue morphogenesis. For example, in CCF-mediated 4D printed degradable hydrogel scaffolds, encapsulated cells actively remodel and deform the matrix by cytoskeletal contraction, resulting in intricate shape changes such as curling, folding, and buckling throughout culture. These hydrogels are first designed to be structurally supportive but permissive, followed by progressive breakdown that enhances cell-cell contacts and contractile forces, eventually leading in scaffold-free, self-organized tissue constructions. This technique closely resembles natural morphogenetic processes, in which tissue architecture originates from coordinated cellular forces rather than external indicators. Importantly, the material structure plays a critical role in facilitating these transitions. Crosslinking density, degradation kinetics, and microgel architecture all play a role in balancing mechanical resistance and deformability, deciding whether cell-generated forces may cause macroscopic shape changes. Rapidly degradable and mechanically adaptable hydrogels, for example, promote increased cellular condensation and anisotropic contraction, resulting in programmable morphogenesis. Conversely, heavily crosslinked or structurally inflexible networks may inhibit cell-driven deformation, restricting dynamic remod-

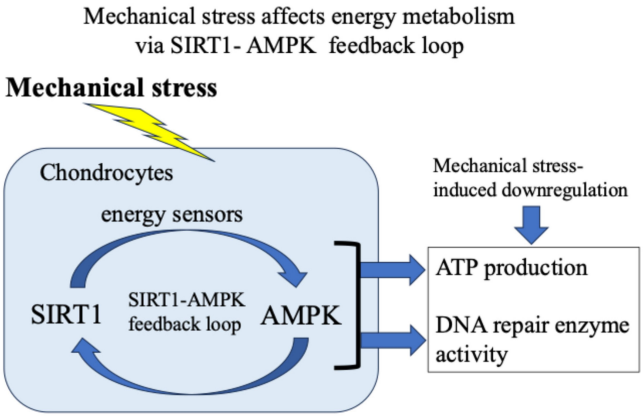

Fig. 1. Energy metabolism (ATP generation) and DNA repair enzyme activity caused by mechanical stress through a SIRT1–AMPK feedback loop. Reproduced with permission [35], MDPI.

elling (Fig. 1) [35,73].

Immuno-Instructive Biomaterials Coupling Mechanics and Immune Modulation

Immuno-instructive biomaterials developed systems intended to actively modulate host immune responses to improve functional tissue regeneration, rather than just reducing immune recognition. Unlike traditional biocompatible materials that seek to be immunologically inactive, immuno-instructive biomaterials utilize immune-tissue interactions as a primary catalyst for restorative results [74]. Post-implantation, immune responses, especially those mediated by innate immune cells, regulate angiogenesis, progenitor cell recruitment, ECM remodelling, and long-term tissue integration. Dysregulated or prolonged inflammation results in fibrotic encapsulation and subsequent implant failure [75,76]. The rational design of biomaterials that can modulate immune cell phenotype, cytokine production, and temporal inflammatory patterns has been made possible by recent developments in materials science. Materials with integrated biochemical signals, mechanical characteristics, degradation kinetics, and surface architecture can actively control the activity of immune and non-immune cells to form regenerative microenvironments [77]. Improved tissue repair across multiple applications, including bone, cartilage, vascular, and soft-tissue regeneration, is achieved by immuno-instructive biomaterials, which guide immune responses toward pro-healing pathways. Therefore, to produce next-generation regenerative therapeutics, it is essential to understand the processes underpinning biomaterial-immune interactions [78,79].

Biomaterial–Immune Cell Interactions

Proteins quickly bind to biomaterial surfaces after implantation, producing a temporary matrix that controls immune cell adhesion and activation. This is the first step in the host immunological response that biomaterials initiate. The way innate immune cells including dendritic cells (DCs), monocytes, and neutrophils interact with the biomaterial is determined by this adsorbed protein coating. Surface chemistry, wettability, stiffness, and degradation byproducts are some of the material's physicochemical characteristics that have a significant impact on immune cell recruitment and functional polarization [79].

The secretion of cytokines, chemokines, and growth factors by macrophages regulates inflammation, angiogenesis, and ECM remodelling, and plays a pivotal role in modulating immunological responses generated by biomaterials (Fig. 2) [80]. Another important role that DCs play is in regulating immunological tolerance or activation via detecting material-associated signals and bridging the gap between innate and adaptive immunity. Moreover, there is emerging evidence that biomaterials can influence phagocytosis, antigen presentation, and cytokine generation via modifying immune cell metabolism and mechanotransduction pathways [81,82].

Nowadays, immuno-instructive biomaterials are engineered to actively manage these immunological interactions, instead than just enduring them. Techniques that allow for the regulated release of immunomodulatory substances, the presentation of bioactive ligands, and customizable degradation patterns allow for the modulation of immune responses throughout time. Tissue integration and long-term regeneration success can be enhanced by the utilization of biomaterial-immune cell interactions, which promote regulated inflammation and constructive remodelling. Delineating the cellular landscape of AL tissues with focus on macrophage and neutrophil subpopulations, Wen *et al*. [83] (2025) used single-cell RNA sequencing (scRNA-seq) to investigate immune-related autophagy in aseptic loosening (AL) of biomaterial bone implants. Results showed that reduced Ctsb expression was associated with increased autophagic activity, increased macrophage apoptosis, and impaired osteoblast differentiation; the study also found that the autophagy-associated gene Ctsb was significantly decreased, mostly in macrophages. Ctsb was pro-

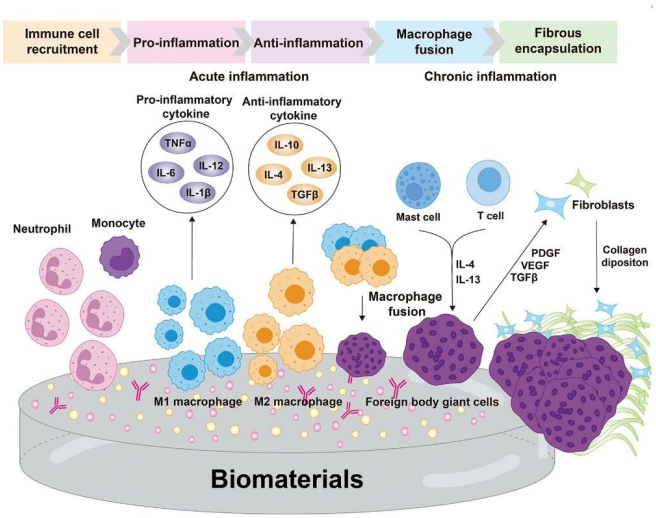

Fig. 2. Response to foreign bodies. The foreign body reaction starts when the implant interacts with host bodily fluids, such as blood, lymph, and wound exudate, resulting from the uncontrolled, spontaneous adsorption of host proteins onto the implant surface. The resultant protein-modulating surface is covered with diverse protein species of differing shapes, and the host cells involved in standard wound healing interact with this atypical adsorbent protein layer. Neutrophils infiltrate the transplant site within hours, responding by synthesizing cytokines, chemokines, reactive oxygen species, and other enzymes, subsequently leading to the recruitment of tissue-resident macrophages and undifferentiated monocytes to the wound area. Thereafter, monocytes develop into M1 macrophages, which are involved in the acute phase of inflammation. M1 macrophages develop into M2 macrophages after a few days. T cells and mast cells secrete cytokines that enhance the development of foreign body giant cells (FBGCs). FBGCs secrete fibroblast recruitment factors, prompting the development of capsules surrounding biomaterials by collagen deposition. Over time, a strong collagenous fibrotic capsule develops around the implant, effectively separating it both physically and physiologically from the host tissue. Reproduced with permission [80] 2024, Wiley Advanced.

posed as a possible therapeutic target when these changes were found to be mechanistically associated with periprosthetic osteolysis and the course of AL. This suggests that macrophage-specific autophagic dysregulation is a fundamental pathogenic event. In 2023, a study was conducted by Wang *et al.* [84] about the use of multiscale biomaterials for targeted immune activation. The focus was on results concerning safety and effectiveness. Compared with traditional small-molecule or macromolecular agonists, the investigation showed that nano to macroscale biomaterials considerably increased immunostimulatory efficacy while decreasing systemic adverse effects. Strong receptor activation resulted from the efficient delivery of agonists to endo/lysosomal compartments or the cytoplasm via nano/microscale systems for intracellular targets.

Engineered biomaterials served as transporters and essential immunostimulatory components for surface receptors by directly engaging immune cell membranes. Biomaterial-based approaches revealed a higher therapeutic index and more efficient immune activation, highlighting its promising future use in immunotherapy and vaccination [84]. Pure titanium (Ti), titanium alloy (TiAlV), 316L stainless steel (SS), and polyetheretherketone (PEEK) are some of the most used orthopedic materials, and in 2023, Avery *et al.* [85] studied the immunological response to these materials in both human and laboratory environments. In comparison to Ti and TiAlV, the results showed that PEEK and SS considerably increased the recruitment of neutrophils, pro-inflammatory macrophages, and $CD4^+$ T cells. There was an increase in elastase, myeloperoxidase, and neutrophil extracellular trap formation in neutrophils that were exposed to PEEK and SS. When compared to Ti substrates, macrophages grown on PEEK, SS, and TiAlV exhibited less Th2/Treg differentiation and more Th1/Th17 polarization. Although both PEEK and SS were clinically biocompatible, the immune response to PEEK and SS was more strongly pro-inflammatory than that to titanium-based materials. This indicates that the composition of the material has a significant impact on the severity of inflammation and the potential of fibrous encapsulation.

Macrophage Polarisation Beyond M1/M2

The intricacy of macrophage activity *in vivo* is not addressed by the classic binary categorization of polarization into pro-inflammatory M1 and anti-inflammatory M2 phenotypes. The activation states of macrophages can be changed in response to mechanical signals, changes in the ECM, metabolic demands, and cytokine gradients. Macrophages in regenerative microenvironments often exhibit a combination of inflammatory resolution, angiogenesis, and tissue remodelling characteristics (Fig. 3) [86]. By manipulating these environmental cues, immunoinstructive biomaterials have the potential to influence macrophage activity. Macrophage cytoskeletal architecture

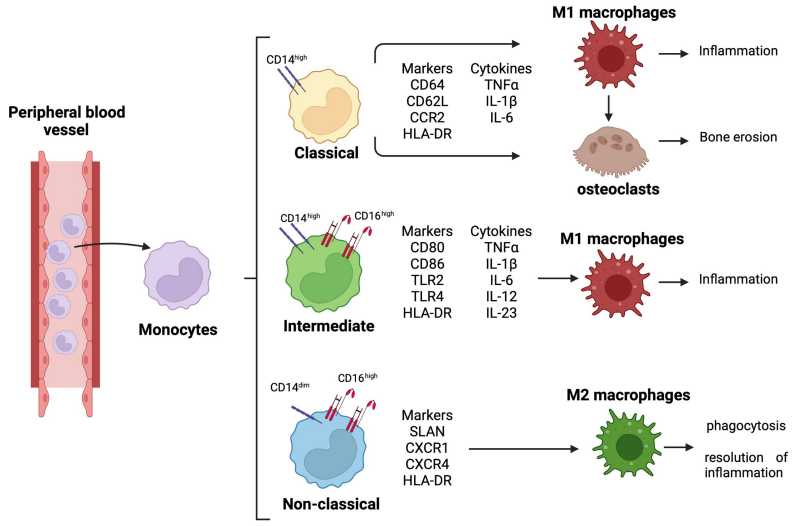

Fig. 3. Monocyte differentiation and related role in RA pathogenesis. Differentiation of circulating monocytes in their three subsets, classical ($CD14^{high}$), intermediate ($CD14^{high}CD16^{high}$), and non-classical ($CD14^{dim}CD16^{high}$) monocytes. Classical monocytes can differentiate into pro-inflammatory macrophages and osteoclasts, contributing to synovial tissue inflammation and bone erosion; intermediate monocytes differentiate into pro-inflammatory macrophages contributing to tissue inflammation; non-classical monocytes differentiate into anti-inflammatory macrophages promoting phagocytosis and resolution of inflammation [Reproduced from Cutolo *et al*. [86], 2022 under an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY)].

and intracellular signalling pathways are impacted by material stiffness, surface topography, and degradation products, leading to functional states that do not fit standard M1 or M2 criteria. Crucially, macrophage responses must be temporally regulated; debris clearance and progenitor cell recruitment necessitate early inflammatory activity, but chronic inflammation limits regeneration [87,88].

Therefore, instead of using strict phenotypic labels, newer methods place more emphasis on the functional outputs of macrophages, including their cytokine secretion patterns, matrix remodelling capabilities, and interactions with stem cells. An approach to immune-guided tissue regeneration that is more physiologically relevant would be biomaterials that may dynamically teach macrophage activity throughout the healing process [89]. Using a model of sepsis caused by caecal ligation and puncture (CLP), Han *et al*. [90] (2026) studied the preventive effects of TaohongSiwu Decoction (THSWD) and amygdalin (AMY), the active component of THSWD. *In vivo*, THSWD considerably reduced inflammatory damage to the heart and lungs. According to mechanistic investigations, AMY is an important bioactive component that inhibits the RAGE/NF-κB/MAPK signalling pathway by directly targeting RAGE. In septic mice, AMY significantly decreased the expression of pro-inflammatory cytokines and blocked M1 macrophage polarization. Although co-administration with the RAGE inhibitor FPS-ZM1 did not result in additive effects, indicating that RAGE is the primary target of AMY, it was shown that AMY inhibited RAGE-mediated LPS-induced M1 polarization in RAW 264.7 cells and BMDMs *in vitro*. Results show that AMY inhibits pro-inflammatory macrophage polarization through RAGE-dependent mechanisms, which in turn mediates anti-septic effects. Fouad *et al*. [91] assessed ertugliflozin's (Ertu) therapeutic potential in a rat model of ulcerative colitis produced by acetic acid in 2025. Ertu significantly improved the visual and histopathological damage to the colon, decreased the expression of NF-κB p65 and miR-155, and changed the polarization of macrophages to an anti-inflammatory M2 phenotype, as shown by increased levels of CD206, Fizz-1, Ym-1, Arg-1, and IL-10, and decreased levels of CD86, MCP-1, TNF-α, IL-1β, and iNOS. Also, by increasing claudin-1, occludin, and ZO-1 expression, Ertu restored the integrity of the epithelial barrier and reduced BAX and increased BCL2 expression, it exhibited anti-apoptotic actions. Remarkably, the anti-inflammatory and mucosal protective effects were mediated through regulation of NF-κB/miR-155 signalling and macrophage polarization, as the maximum dosage (10 mg/kg) showed effectiveness equivalent to sulfasalazine. Long *et al*. [92] showed in 2025 that PDNV, which were produced from *Portulaca oleracea*, considerably reduced atopic dermatitis (AD) by reducing NF-κB and STING signalling in inflamed tissues and influencing macrophage polarization toward the M2 phenotype. *In vivo*, PDNV therapy ameliorated AD symptoms while reducing inflammatory responses. Microneedles made of soluble hyaluronic acid and Portulaca polysaccharides were developed to improve the mechanical stability and therapeutic effectiveness of transdermal administration. A promising nanotherapeutic approach for the treatment of Alzheimer's disease was shown by the synergistic effects of nanovesicles and microneedles, which revealed

markedly improved anti-inflammatory effects.

Surface Topography and Immune Modulation

To modulate the immune system independently of soluble substances, surface topography is an effective design element. The adhesion, shape, and mechanotransduction signalling of immune cells are all directly impacted by surface characteristics at the micro- and nanoscale. Topographical signals can modulate cytoskeletal tension, focal adhesion formation, and subsequent inflammatory signalling in DCs and macrophages [93]. Research has shown that surfaces with nanostructures or hierarchies can limit the dispersion of immune cells, which in turn reduces excessive inflammatory activation [94]. On the other hand, surfaces with aligned or anisotropic topographies encourage the pro-regenerative elongated macrophage morphologies [95]. The spatial organization and immune cell infiltration within biomaterials are further impacted by microgrooves, pores, and connected patterns. In order to shape immunological responses at the material interface, these physical cues stimulate cytoskeletal remodelling and integrin-mediated signalling pathways [96].

In addition to biochemical and mechanical inputs, topographical cues offer steady and long-term signals that modulate the immune system. The goal of immuno-instructive biomaterials is to regulate the immune response in space and time by engineering the surface architecture across different length scales. This control may then be used to promote angiogenesis, ECM deposition, and constructive tissue remodelling [97]. Using adjustable nano, submicro, and microscale wrinkled multilayer coatings, Chavda *et al*. [98] (2026) showed that optimized surface topography significantly affects DC immune programming. An immunogenic mature DC phenotype was designed by microscale topographies, which was marked by increased levels of IL-6, IL-12, TNF-α, co-stimulatory marker expression, NF-κB activation, and robust T-cell activation. Nanoscale wrinkles and flat surfaces maintained DC immaturity with high antigen uptake and minimal activation, but submicroscale patterns induced a largely mature, homeostatic/tolerogenic profile with elevated TGF-β and IL-10 levels and decreased cross-presentation. This research proves that DC functional polarization is directed by surface design and emphasizes the use of topography-engineered biomaterials as a scalable method for controlling immune responses in immunotherapy. To compare osteoblast responses to acid-etched microrough titanium surfaces with machined smooth surfaces, Komatsu *et al*. [99] conducted genome-wide RNA sequencing in 2023. While there was a strong correlation (r = 0.975) between the overall gene expression profiles, microrough surfaces caused selective modulation of transcription, leading to an upregulation of 1.38% of the genes and a downregulation of 0.37%. Immune response, stimulus-response, and plasma membrane signalling pathways were enriched in upregulated genes. The development of stress fibres and focal adhesions was stimulated by microrough surfaces, which also elevated the production of ECM-related glycoproteins such as laminin, fibronectin, CD36, and thrombospondin. There was a decrease in proliferation and an acceleration of differentiation, as shown by the higher levels of proliferation-associated markers PCNA and cyclin D1. Transcriptional processes linked to osteoblast development and functional adaptability were triggered by microrough titanium surfaces, which in turn triggered different programs involving the immune system, cytoskeleton, and ECM.

Osteoimmunology and Tissue-Specific Responses

The field of osteoimmunology offers a framework for the development of biomaterials that are tailored to specific tissues and highlights the importance of immune-bone communication in the process of skeletal regeneration [100]. Through cell-cell contacts and cytokine communication, immune cells such as neutrophils, macrophages, and T cells directly control bone remodelling and osteogenesis. When the immune system is in balance, it promotes angiogenesis and osteoblast development, but when inflammation is persistent, it hinders bone regeneration [101]. Since skeletal tissue has its own distinct immunological and mechanical milieu, immuno-instructive biomaterials used to regenerate bone must be customized accordingly. The behaviour of immune cells and the osteogenic results can be affected by material stiffness, degradation kinetics, and ion release patterns. An important aspect of immune regulation in bone regeneration is the function that signals originating from macrophages play in coordinating the activity of osteoblasts and osteoclasts [94]. In addition to bone, immune responses differ greatly among other tissues including skin, muscle, and cartilage, calling for biomaterial techniques that are reliant on context.

The rational design of biomaterials that control immune responses in coherence with the restorative demands of each tissue is made possible by integrating osteoimmunological principles with tissue-specific immune information. This integration improves translational and clinical outcomes [102]. In 2024, Mu *et al*. [103] proved that BIE, which is made of bone-derived monetite (BM), an inorganic component of bone, directly stimulates osteogenesis and modulates the immunological response to bone loss. BIE promoted intracellular buildup of carbonate hydroxyapatite and accelerated osteogenic differentiation and mineralization of human bone marrow stromal cells, simulating physiological osteoblast mineralization, all without the need of exogenous osteoinductive supplements. In addition, BIE resulted in an immunological milieu that was favourable to bone growth, or pro-osteogenic. In an animal model of a critical-size calvarial lesion, a BM composite (Col-BM) impregnated with collagen type I considerably enhanced the rate of new bone production. These results shown that inorganic bone components have an inherent

ability to promote bone formation and emphasize the importance of the bone ionic environment in regulating osteogenesis and osteoimmunomodulation. Using immunomodulation, Bao *et al*. [104] (2023) enhanced early osseointegration on TiAlV (TC4) by engineering nanocone (NC), nanopolyhedron (NP), and nanoflower (NF) cerium oxide (CeO_2-x) coatings. The formation of M2 macrophage polarization, improved endothelial angiogenesis, and accelerated osteogenic differentiation and mineralization were all seen *in vitro* on surfaces coated with nano-CeO_2-x. Improved M2 polarization, neovascularization, and bone regeneration was validated in an *in vivo* examination of a rat femoral condyle model. The NF morphology showed greater osseointegration. The improved immunomodulatory action of NF was shown to be based on suppression of the PI3K-AKT signalling pathway, according to RNA sequencing. All things considered, the integration of implants and modulation of the immune system were greatly enhanced by nano-structured CeO_2-x coatings, especially NF.

Mechanical Signals on Immune Behaviour

It is becoming increasingly apparent that mechanical signals inside the cellular milieu play an essential role in controlling the activity of immune cells. Macrophages, DCs, and neutrophils are immune cells that monitor and react to mechanical qualities such as viscoelasticity, substrate stiffness, stress relaxation, and dynamic loading [105]. Integrins, focal adhesion complexes, and actin remodelling are involved in the mechanotransduction pathways that these mechanical signals use to affect the adhesion, cytoskeletal architecture, movement, and activation of immune cells [106]. For macrophages in particular, the functional responses to matrix stiffness vary; in general, macrophages are more pro-regenerative and anti-fibrotic in situations with softer matrices, whereas macrophages activate more easily in conditions with higher matrix stiffness [107]. The secretion patterns of cytokines and immune cell metabolism are regulated by mechanical cues, which in turn affect subsequent events including angiogenesis, stem cell application, and the deposition of ECM. Importantly, during tissue healing, immune responses shift over time in reaction to changes in mechanical conditions [108,109].

When it comes to regenerative contexts improperly calibrated mechanical environments can lead to immunological resolution and tissue integration, whereas aberrant signalling can maintain chronic inflammation and impede healing [107]. The significance of integrating mechanical design factors into immuno-instructive biomaterials is emphasized by these findings. By utilizing mechanobiological concepts, biomaterials can be designed to direct immune cell activity towards phenotypes that promote constructive tissue remodelling instead of fibrotic encapsulation [110,111]. In 2026, Fu *et al*. [112] identified miR-322-5p as a key modulator of neurodevelopmental defects produced by maternal immune activation (MIA). miR-322-5p was markedly increased in the prefrontal cortex of MIA children, directly repressing Brain-derived neurotrophic factor (BDNF) production and hence limiting BDNF/TrkB/AKT signalling, resulting in a concomitant decrease in PSD95 levels. These molecular changes were associated with hypoactivity, cognitive impairments, social dysfunction, and impaired sensorimotor gating. Significantly, the inhibition of miR-322-5p or the overexpression of BDNF reinstated signalling pathways and mitigated both behavioural and synaptic impairments, highlighting the role of miR-322-5p-mediated suppression of BDNF as a pivotal mechanism and prospective therapeutic target in MIA-associated neurodevelopmental problems. In 2025, Heir *et al*. [113] discovered the activity-dependent regulation of immunological signalling molecules in the hippocampus and elucidated their functional roles in synaptic modulation. Neuronal silencing with TTX upregulated many immune mediators, while increased activity with gabazine elicited a more limited collection, including interferon-γ (IFNγ). Functional experiments showed IFNγ acutely influenced both glutamatergic and GABAergic synaptic transmission. Additionally, mice lacking IFNγ signalling exhibited modified anxiety-like behaviour in a sex-specific way, namely in males. The findings suggest that immune cytokines, including IFNγ, operate as endogenous regulators of synaptic activity and behaviour under physiological environments.

Designing Scaffolds With Dual Mechanical and Immunomodulatory Functionality

The integration of mechanical and immunological design concepts has resulted in scaffolds that offer dual functionality, offering both biomechanical support and actively modulating immune responses [114]. These scaffolds are designed to exhibit certain stiffness gradients, viscoelastic characteristics, and structural anisotropy, while also integrating immunomodulatory biochemical signals. This comprehensive method allows accurate regulation of immune cell recruitment, activation, and temporal phenotypic changes during the healing process [115]. The stiffness of materials and their degradation kinetics may be customized to align with the mechanical properties of native tissue while adapting to the progression of tissue development. Simultaneously, surface chemistry, ligand presentation, and micro- or nanoscale architecture can influence immune cell adhesion and signalling. Advanced fabrication techniques, such as hierarchical structure and 3D printing, enable the spatial patterning of immunological and mechanical signals inside a single scaffold [116].

Significantly, dual-functional scaffolds reduce dependence on external immunosuppressive drugs by using intrinsic immune systems. These biomaterials enhance angiogenesis, progenitor cell differentiation, and matrix remodelling by aligning mechanical stability with regulated immunological regulation. This design paradigm signifies

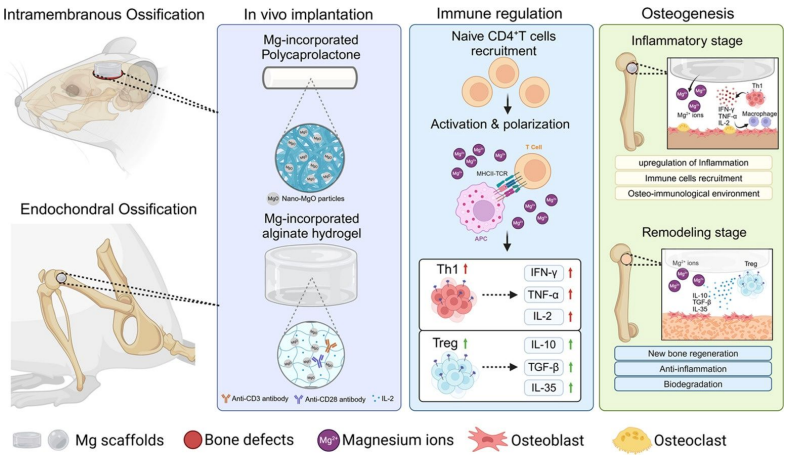

Fig. 4. Schematic depiction illustrating the function of magnesium-based biomaterials in improving bone lesion repair through the control of CD4$^+$ T cell-mediated immune responses. Reproduced from Liu *et al*. [118], 2026 under an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY-NC-ND)].

a transition from passive structural support to actively instructional scaffolds that coordinate both immune and regenerative processes [117]. Liu *et al*. [118] showed in 2026 that regulated administration of Mg^{2+} enhances osteogenesis by modulating CD4$^+$ T cell polarization. A balanced pro-/anti-inflammatory microenvironment was established and CD4$^+$ T cell activation and proliferation were greatly enhanced at optimal Mg^{2+} concentrations, which also promoted Th1 and Treg differentiation. The activity of alkaline phosphatase and calcium deposition in MSCs were both improved by conditioned media from Mg^{2+}-stimulated CD4$^+$ T cells, which had the dual impact of stimulating osteogenesis and counteracting the inhibitory effects of high Mg^{2+} levels. T cell activator-crosslinked Mg-alginate hydrogels sped up bone regeneration by reducing early inflammation and improving long-term Treg regulation, while 1% MgO-doped PCL scaffolds *in vivo* enhanced membrane ossification in brain defects by sustaining Mg^{2+} release. The results show that a critical process in bone regeneration caused by Mg^{2+}-functionalized biomaterials is CD4$^+$ T cell-mediated osteoimmunomodulation (Fig. 4).

Xu *et al*. [119] developed a hydrogel meniscus scaffold in 2025 that was multifunctional, including a meniscus that was stronger mechanically, had more antioxidant capacity, and could modulate the immune system. A hypoxia-mimetic milieu was established by the carboxyl-rich network of the scaffold, which allowed for effective iron chelation. This microenvironment then activated HIF-1α signalling, balanced pro-/anti-inflammatory responses, and enhanced oxidative resistance. Regeneration of the meniscus, as well as chondrocyte survival and matrix deposition, were all much improved by this milieu.

Peripheral blood MSCs showed better regeneration performance under low-oxygen settings compared to bone marrow MSCs, and *in vivo* and *in vitro* studies revealed that the hypoxia-driven immune modulation improved the quality of the tissue-engineered meniscus. The immune system was able to govern meniscus regeneration primarily to the iron-chelation-induced hypoxic niche (Fig. 5). A multifunctional scaffold was developed in 2026 by Pant *et al*. [120] to deal with post-operative tumour recurrence and metastatic bone deformities. It consisted of 3D-printed curcumin-infused PLA coated over amine-functionalized TiO_2-doped mesoporous bioactive glass (MBG). The scaffold showed high antibacterial action against both Gram-positive (~90%) and Gram-negative (~85%) pathogens, as well as fast *in vitro* bioactivity and sustained curcumin release, leading to around 90% cell death in osteosarcoma. At the same time, TiO_2-doped MBG greatly improved the osteogenic differentiation of MSCs generated from adipose tissue, as shown by an enormous increase in alkaline phosphatase activity and calcium mineralization ($p < 0.0001$), which was improved by regulated ROS release and an elevation of early and late osteogenic markers. Together, the scaffold's anti-tumour, antibacterial, and pro-osteogenic properties lend credence to its efficacy as a post-resection bone regeneration technology.

In 2026, a study by Vemuri *et al*. [121] showed that exosomes from synovial fluid-derived mesenchymal stem cells (SF-MSCs) greatly improved cartilage repair in a model of rat osteoarthritis. In comparison to monotherapies, the combination therapy outperformed them by week 8, reducing the amount of cartilage defects by 85.3% and increasing bone density by 57.8%. Histological studies validated increased ECM deposition and superior cartilage regeneration, while qPCR showed a significant rise of osteogenic markers. This research lends credence to the idea that a cell-supported exosome platform can boost regeneration efficacy via paracrine signalling, immunomodulatory processes, and coordinated differentiation, and could one day be used as a less invasive treatment for osteoarthritis. To improve tendon-bone interface regeneration, Zeng

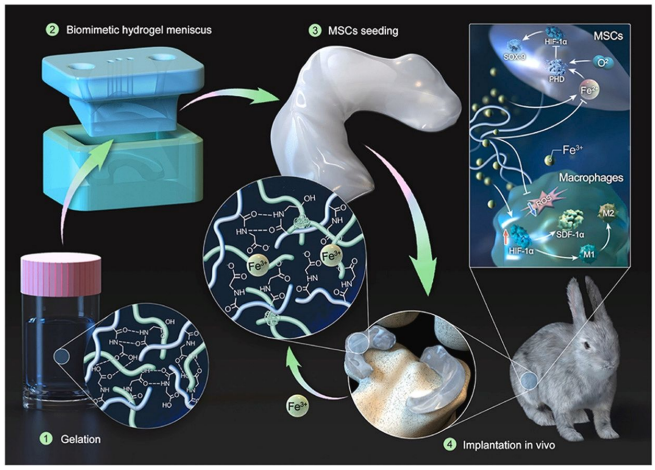

Fig. 5. Schematic representation of the study: synthesis of a multifunctional PACG/CS composite hydrogel meniscus scaffold through ionic crosslinking, UV-induced semi-interpenetrating network formation, and personalized injection molding. The scaffold shows biomimetic heterogeneity, exceptional mechanical strength, self-repair capabilities, and anti-inflammatory and antioxidant effects. Following implantation, iron ion chelation provides a hypoxia-mimicking milieu that promotes meniscal regeneration. [Reproduced from Xu *et al.* [119], 2025 under an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY-NC-ND)].

et al. [122] (2026) developed a 3D-printed PEI-based scaffold (P-$CaSiO_2$-ZnO) that could release Si, Ca, and Zn ions under controlled conditions. The scaffold successfully modulated inflammatory responses *in vitro* while promoting osteogenic, chondrogenic, and tenogenic development. Compared to controls, it greatly increased tendon-bone integration and mechanical strength *in vivo* by speeding up new bone production, improving collagen organization, and restoring the fibrocartilaginous transition zone. These findings show that the tendon-bone contact can be structurally and functionally improved using ion-mediated immunomodulation in conjunction with multi-lineage tissue induction (Fig. 6).

An exact graded cartilage-to-bone architecture was achieved in BioGraOstO, a 3D bioprinted osteochondral scaffold, in 2025 by Yang *et al.* [123] using DLP technology. The multilayered structure showed regulated biodegradation, minimum swelling (<10%), tuneable mechanical characteristics (1.35–17.29 kPa), and interfaces that were well-integrated. Histological and molecular investigations validated the scaffold's ability to promote region-specific differentiation of bone marrow stem cells (BMSCs) into osteogenic and chondrogenic lineages *in vitro*. After 12 weeks, BioGraOstO considerably outperformed acellular controls in a rat model of osteochondral defect, regenerating nearly all of the articular cartilage and subchondral bone. These findings showed that techniques including graded biomimetic bioprinting are efficient in repairing osteochondral defects. In a rabbit model of full-thickness chondral lesion, Torres-Torrillas *et al.* [124] (2025) showed that PRGF, ASCs, or a combination of the two greatly improved subchondral bone and cartilage repair after intraosseous (IO) infiltration. At both 56 and 84 days, the groups treated with IO had better histological repair than the control group that received only IA PRGF. The group that received a combination of PRGF and ASC showed the most significant healing of the cartilage. The results revealed that compared to intra-articular therapy alone, IO administration leads to more persistent and successful osteochondral regeneration, especially when PRGF and ASCs are combined.

Translational Considerations

In Vitro Versus In Vivo Discrepancies

A big challenge in translating immuno-instructive and mechanically dynamic biomaterials is the disparity between *in vitro* and *in vivo* results, which persists despite notable improvements in biomaterial design [110]. Although *in vitro* models allow for the controlled examination of certain cell-material interactions, they frequently ignore the intricacy of immunological responses, mechanical loading conditions, and tissue heterogeneity that occur *in vivo*. Regenerative results in live tissues are determined by a complex interplay of mechanical conditions, vascularization, immune cell populations, and dynamic cytokine gradients, all of which are absent in simplified culture methods [125,126]. Various factors, such as variations in cell source, activation state, and temporal exposure to material cues, can make it difficult to reliably anticipate *in vivo* responses based on immune cell behaviour observed *in vitro*. When it comes to the dynamic mechanical and biochemical environment that is faced during tissue healing, static culture conditions just fail to address it. So, biomaterials with promising mechanobiological or immunomodulatory properties in the lab could cause fibrosis or inflammation when used in humans [127]. To overcome this challenge,

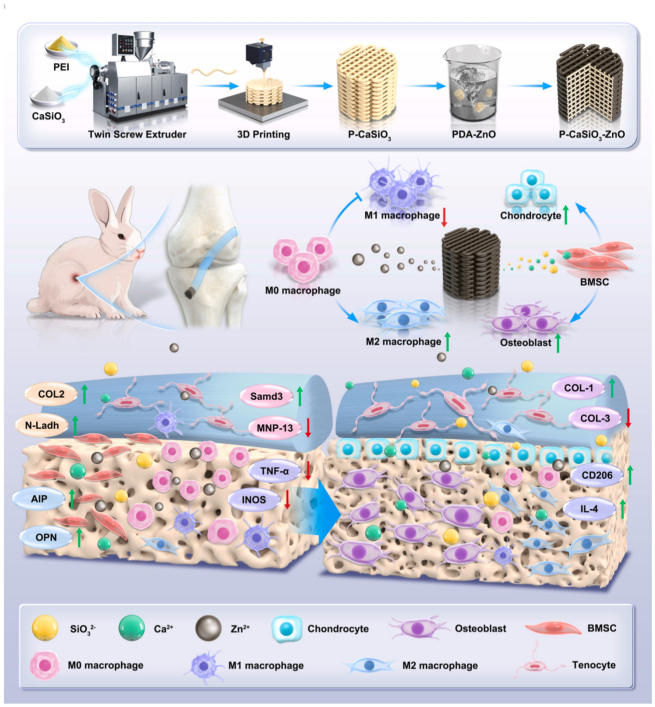

Fig. 6. Schematic illustration depicting the fabrication process of the P-CaSiO$_3$-ZnO composite scaffold and its ensuing application in promoting regeneration at the tendon-bone interface. [Reproduced from Zeng *et al*. [122], 2026 under an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY)].

we need to develop preclinical models that incorporate immunological, stromal, and progenitor cells in a more realistic setting, such as organotypic platforms, dynamic bioreactors, and co-culture systems. To improve prediction accuracy and decrease translational failure, it is also necessary to develop better *in vivo* models that take into consideration immunological differences between species [128].

Biomaterial Degradation and Host Immune Response

Biomaterial degradation significantly affects the modulation of host immune responses and long-term regenerative effects. The behaviour of immune cells is regulated by degradation kinetics, which determine mechanical integrity, byproduct buildup, and the timing of bioactive signalling release. Prolonged degradation might extend foreign body responses and impede tissue integration, whereas rapid degradation may undermine structural support and trigger acute inflammation [129]. The chemical composition of polymers affects the immunological responses of their degradation products. For example, polyesters like PLGA and PLA produce acidic byproducts that can decrease local pH, promoting pro-inflammatory macrophage (M1) polarization and cytokine secretion, whereas natural polymers such as collagen and chitosan generate bioactive fragments that enable anti-inflammatory (M2) phenotypes and tissue remodelling. Likewise, synthetic polymers like PEG are generally innocuous but can provoke immunological responses based on their molecular weight and functionalization. Degradation-derived ions, oligomers, and metabolites can directly influence immune cell activation by modifying redox balance, osmolarity, and pH, therefore affecting cytokine release and ECM remodelling. Furthermore, the particle size and solubility of breakdown products are pivotal, since smaller pieces are more easily absorbed by macrophages, which may induce inflammasome activation. A dynamic feedback loop arises in which immune cells actively promote biomaterial destruction by phagocytosis and enzymatic activity, hence influencing the local immunological environment [130,131]. Consequently, accurate alignment between degradation profiles and immune modulation is imperative for optimum tissue regeneration. Developing immuno-instructive biomaterials with adjustable and foreseeable degrading properties enables regulated immune regulation across various stages of recovery. A thorough assessment under physiologically pertinent mechanical and immunological circumstances is essential to guarantee safety, effectiveness, and translational reproducibility in clinical applications [132].

Regulatory and Clinical Challenges

Many practical and regulatory challenges stand in the way of the clinical translation of biomaterials that are both mechanically dynamic and immuno-instructive. Regulatory classification and approval routes are made more complicated by the multifunctional nature of these materials, which combine structural support, immunomodulation, and, in some instances, biological activity. It takes early regulatory involvement and thorough evaluation to decide

if a product is a medical device, a combination product, or an advanced therapy [78,133]. Immune responses and mechanical performance differ among models and experimental settings, making it difficult to standardize preclinical testing. For products that aim to actively alter immune function, regulatory bodies want strong proof of safety, repeatability, and durability. Translation is further complicated by manufacturing scalability, batch-to-batch consistency, and quality control, particularly for materials made utilizing sophisticated fabrication techniques [134]. There is already a lot of ambiguity surrounding treatment outcomes due to patient heterogeneity, illness circumstance, and unpredictability at the implantation location. Material scientists, immunologists, physicians, and regulatory specialists will need to work together interdisciplinary to solve these problems. For immuno-instructive biomaterials to move forward from experimental systems to authorized regenerative therapies, it is essential to establish standardized evaluation frameworks and clinically meaningful objectives [74].

Future Perspectives

The future of immuno-instructive biomaterials lies in the development of personalized and adaptive systems capable of responding to patient-specific mechanical and biological signals while evolving throughout the regenerative process. Increasing evidence shows that biomaterial performance is strongly influenced by inter-individual variability, including immune profiles, genetic background, age, disease state, and tissue mechanics, highlighting the limitations of one-size-fits-all designs [135]. To address this, next-generation biomaterials are being engineered with adaptive features such as stimuli-responsive degradation, dynamic ligand presentation, and tunable mechanical properties, enabling real-time interaction with the host microenvironment. Such adaptability can guide immune responses across different stages of healing, from initial inflammation to tissue remodelling, thereby improving long-term regeneration and integration. These advancements are particularly important in aging and diseased microenvironments, where regeneration is compromised by immunological dysregulation, impaired mechanosensing, chronic inflammation, and altered ECM composition. Age-related immune changes and diseases such as diabetes, fibrosis, osteoarthritis, and osteoporosis create hostile biochemical and mechanical conditions that hinder scaffold integration and tissue repair. In this context, biomaterials with optimized immuno-mechanical properties offer strong translational potential by restoring pro-regenerative signalling and recalibrating immune responses. Designing such systems requires careful consideration of immunosenescence, macrophage dysfunction, and disease-specific inflammatory markers [136]. Parallel to these developments, the integration of immuno-instructive design with advanced manufacturing technologies is transforming the field. Techniques such as 3D and 4D bioprinting enable the fabrication of heterogeneous, hierarchical scaffolds with precise spatial control over mechanical properties, cellular organization, and immunomodulatory cues. Multi-material printing, digital design frameworks, and scalable fabrication methods further support reproducibility and clinical translation. Emerging trends also highlight the growing importance of smart polymers and multi-responsive biomaterials. In particular, 4D-printed shape memory polymer (SMP) composites enable time-dependent structural transformations in response to external stimuli. Recent advances in near-infrared (NIR)-responsive 4D-printed SMP systems (2026) demonstrate the potential for remote activation, controlled shape recovery, and real-time imaging, enabling minimally invasive deployment of biomedical constructs such as stents, scaffolds, and nerve conduits. These systems integrate therapeutic and diagnostic functions, allowing in situ monitoring of material performance [137]. Despite these advances, several key challenges must be addressed to enable clinical translation. The most critical limitation is the mismatch between simplified *in vitro* models and complex *in vivo* regenerative environments, where the interplay between mechanics, immunity, and tissue remodelling is not fully captured. This is closely followed by patient-specific heterogeneity, which complicates the design of universally effective biomaterials. Another major challenge is achieving precise spatiotemporal control over coupled mechanical and immune signalling, as current systems often lack the ability to dynamically adapt to evolving biological conditions. In addition, manufacturing scalability and reproducibility, particularly for complex and multi-material systems, remain significant barriers. Finally, regulatory approval and long-term safety, including biodegradation behaviour and immune compatibility, are essential considerations for clinical implementation [138]. Emerging strategies provide promising solutions to these challenges. The development of smart, stimuli-responsive biomaterials, including 4D-printed systems, enables dynamic adaptation to changing microenvironments. Technologies such as NIR-responsive biomaterials allow remote control and real-time monitoring, while advances in computational modelling, artificial intelligence, and biomanufacturing are expected to accelerate the rational design of personalized and adaptive systems. Collectively, these developments point toward a future in which biomaterials function as intelligent, adaptive platforms capable of sensing, modulating, and coordinating immune and mechanical signals. Such innovations hold significant promise for advancing precision regenerative medicine, enabling more predictable, durable, and patient-specific therapeutic outcomes [139,140].

Conclusions

Biomaterials that are immuno-instructive and mechanically dynamic represent a paradigm shift in regenerative medicine, as they transition from passive structural support to the active regulation of cell fate within intricate

tissue microenvironments. Native tissues show a dynamic interaction between immune-mediated repair processes and matrix rigidity, viscoelasticity, and stress relaxation, which is characterized by tightly coordinated mechanical and immunological signals. In order to achieve successful regeneration, biomaterials must not only replicate the mechanical properties that are evolving but also precisely regulate the behaviour of immune cells in a context-dependent manner.

Mechanical cues modulate stem cell lineage commitment through integrin signalling, cytoskeletal organization, and YAP/TAZ activation, as evident in the advancements in dynamic hydrogels, tuneable stiffness systems, and mechanotransductive pathway targeting. Simultaneously, immuno-instructive designs have demonstrated that immune responses are not limited to the simplistic M1/M2 paradigm. They encompass spatiotemporally governed macrophage phenotypes as well as tissue-specific immune associations, including osteoimmunological mechanisms. Furthermore, there is growing evidence that mechanical properties themselves have an impact on immune polarization, emphasizing a critical convergence between mechanobiology and immunology. The integration of dual-function scaffolds, which can combine immune modulation with adaptive mechanical behaviour, provides promising strategies for the regeneration of complex tissues, particularly in the restoration of bone and cartilage. Nevertheless, there are still translational challenges that must be addressed, such as the difference between *in vitro* and *in vivo* models, the kinetics of biomaterial degradation, the long-term host responses, and regulatory considerations. The development of biomaterials that are adaptive and personalized, and that can adapt to patient-specific, geriatric, or diseased microenvironments, is likely to be a determining factor in future advancements. The design of next-generation regenerative systems will be further accelerated by the convergence of immuno-engineering, advanced bioprinting, and smart manufacturing technologies with mechanically dynamic platforms. In the end, it will be imperative to possess a comprehensive comprehension of the interaction between immunity and mechanics to develop biomaterials that not only facilitate tissue repair but also actively coordinate functional regeneration.

List of Abbreviations

ECM, extracellular matrix; MMPs, matrix metalloproteinases; MSCs, mesenchymal stem cells; FAK, focal adhesion kinase; YAP, Yes-associated protein; TAZ, transcriptional co-activator with PDZ-binding motif; LINC, Linker of Nucleoskeleton and Cytoskeleton; CCFs, cell contractile forces; FBGCs, foreign body giant cells; scRNA-seq, single-cell RNA sequencing; AL, aseptic loosening; Ti, titanium; TiAlV, titanium alloy; SS, stainless steel; PEEK, polyetheretherketone; CC BY, Creative Commons Attribution License; CLP, caecal ligation and puncture; THSWD, TaohongSiwu Decoction; AMY, amygdalin; AD, atopic dermatitis; DC, dendritic cell; BM, bone-derived monetite; NC, nanocone; NP, nanopolyhedron; NF, nanoflower; CeO_2−x, cerium oxide; MIA, maternal immune activation; BDNF, Brain-derived neurotrophic factor; IFNγ, interferon-γ; MBG, mesoporous bioactive glass; SF-MSCs, synovial fluid-derived mesenchymal stem cells; BMSCs, bone marrow stem cells; IO, intraosseous; SMP, shape memory polymer; NIR, near-infrared; AIP, Aryl hydrocarbon receptor-interacting protein; ALT, Alanine transaminase; AMPK, Adenosine monophosphate-activated protein kinase; AST, Aspartate transaminase; ATP, Adenosine triphosphate; BDNF, Brain-derived neurotrophic factor; BMDMs, Bone marrow-derived macrophages; CD80, Cluster of differentiation 80; COL-3, Collagen type III; CXCR4, C-X-C motif chemokine receptor 4; DLP, Dendritic-like polymer; DNA, Deoxyribonucleic acid; ERK, Extracellular signal-regulated kinase; FAK, Focal adhesion kinase; FBGCs, Foreign body giant cells; HIF-1α, Hypoxia-inducible factor-1α; HLA-DR, Human leukocyte antigen-DR isotype; iNOS, Inducible nitric oxide synthase; IL-6, Interleukin-6; MAPK, Mitogen-activated protein kinase; MNP-13, Mn-based nanoparticle 13; N-Ladh, N-terminal Ladh/Lysyl aldehyde (Ladh); NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; PDGF, Platelet-derived growth factor; PEG, Polyethylene glycol; PEI, Polyethylenimine; PLA, Polylactic acid; PLGA, Poly (lactic-co-glycolic acid); PRGF, Plasma rich in growth factors; qPCR, quantitative real-time polymerase chain reaction; RAGE, Receptor for advanced glycation end products; ROCK, Rho-associated coiled-coil containing protein kinase; ROS, reactive oxygen species; SIRT1, Sirtuin 1; SLAN, Sialic acid-binding immunoglobulin-like lectin; TGF-β, Transforming growth factor β; TLR4, Toll-like receptor 4; TNF-α, Tumor necrosis factor α; VEGF, Vascular endothelial growth factor; Samd3, sterile alpha motif domain containing 3.

Availability of Data and Materials

Not applicable. No data was generated for the content described in this review manuscript.

Author Contributions

VP and AS: Conceptualization, data curation, formal analysis, investigation, methodology, writing—original draft, writing—review & editing. PK: Conceptualization, data curation, formal analysis, visualization, resources, writing—review & editing. All authors read and approved the final manuscript for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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