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Dynamic Nano–Bio Interfaces in Regenerative Medicine: From Molecular Interactions to Tissue-Specific Regeneration

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Abstract

Nanomaterials have emerged as versatile platforms for modulating biological processes and creating advanced interfaces for tissue regeneration. However, their biological behavior is not determined solely by their intrinsic physicochemical properties but evolves dynamically following interaction with the biological environment. This review provides a comprehensive perspective on nano–bio interfaces, emphasizing the mechanisms through which nanomaterials interact with proteins, cellular membranes, intracellular compartments, immune cells, stem cells, and tissue microenvironments. Particular attention is given to the formation and evolution of the protein corona, cellular recognition and uptake, intracellular trafficking, oxidative and inflammatory responses, and interactions with the immune system. The influence of nanomaterial-mediated signals on stem-cell adhesion, proliferation, migration, mechanotransduction, metabolism, and lineage-specific differentiation is further discussed. Tissue-specific applications in bone, cartilage, neural, cardiac, vascular, and skin regeneration are examined to highlight how nanomaterial properties can be adapted to distinct biological and mechanical environments. In addition, the review addresses nanomaterial degradation, persistence, long-term biocompatibility, nanotoxicity, reproducibility, and challenges associated with clinical translation. Emerging strategies involving three-dimensional models, organ-on-chip platforms, single-cell and spatial omics, artificial intelligence, and adaptive nanomaterials are also considered. Overall, this review emphasizes a shift from designing nanomaterials solely for structural support or passive biocompatibility toward the development of dynamic, biologically instructive, and tissue-specific nano–bio interfaces capable of actively regulating cellular and immune responses. Such a mechanistic and predictive approach may facilitate the development of safer and more effective nanomaterials for next-generation regenerative medicine.

Keywords: Nano–bio interface, Nanomaterials, Tissue regeneration, Stem cells, Immune response, Protein corona, Nanotoxicity.

1 | Introduction

Regenerative medicine has emerged as a multidisciplinary field aimed at restoring the structure and function of damaged or diseased tissues through the coordinated use of cells, biomaterials, bioactive signals, and

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engineered microenvironments [1–5]. Unlike conventional approaches that primarily seek to replace damaged tissue, regenerative strategies attempt to recreate the biological conditions required for endogenous repair and functional tissue reconstruction. The success of these approaches, however, depends not only on the intrinsic properties of the cells or biomaterials employed but also on the dynamic interactions that occur immediately after a biomaterial is introduced into a biological environment. At the interface between an engineered material and the surrounding biological system, a complex sequence of molecular, cellular, and immunological events determines how the material is recognized, internalized, degraded, and ultimately integrated into regenerating tissue [4–7].

Nanotechnology has introduced a new dimension to regenerative medicine by enabling the design of materials with structural features and physicochemical properties at length scales comparable to biological macromolecules, cellular receptors, and extracellular matrix components [8]. Nanomaterials can be engineered with precise control over parameters such as particle size, morphology, surface chemistry, charge, hydrophilicity, mechanical properties, and degradation behavior. These characteristics can substantially influence interactions with proteins, cell membranes, intracellular organelles, and immune cells. Consequently, the biological performance of a nanomaterial cannot be understood solely from its bulk composition; rather, it emerges from the complex relationship between its physicochemical characteristics and the biological environment in which it operates [9].

The concept of the nano–bio interface has therefore become central to understanding the biological behavior of nanomaterials. When a nanomaterial encounters a physiological environment, its original surface is rapidly transformed through adsorption of proteins, lipids, ions, and other biomolecules. This process can generate a dynamic biomolecular layer, commonly referred to as the protein corona, which effectively determines the biological identity of the nanomaterial. The resulting interface can influence cellular recognition, membrane adhesion, endocytic uptake, intracellular trafficking, immune activation, and degradation. Importantly, the composition and organization of this interfacial layer are not static but may continuously evolve in response to changes in the surrounding biological milieu. Thus, the biological identity of a nanomaterial may differ substantially from its physicochemical identity as characterized prior to exposure to biological systems [8–12].

Cellular responses to nanomaterials are equally complex and depend on multiple interconnected mechanisms. Following interaction with the cell membrane, nanomaterials may be internalized through distinct endocytic pathways or remain associated with the extracellular environment. Their subsequent intracellular fate may involve trafficking through endosomal and lysosomal compartments, interaction with mitochondria, generation of Reactive Oxygen Species (ROS), alteration of intracellular signaling, or modulation of gene expression. These events can affect fundamental cellular processes, including proliferation, migration, differentiation, metabolism, autophagy, and apoptosis. In regenerative medicine, such interactions are particularly important because subtle changes in cellular signaling can determine whether a nanostructured microenvironment promotes tissue repair or instead induces cellular stress and impaired regeneration [11].

The immune system represents another critical determinant of nano–bio interactions. Nanomaterials introduced into injured tissue are immediately exposed to inflammatory and immune cells that participate in the early stages of tissue repair. Macrophages, neutrophils, dendritic cells, lymphocytes, and components of the complement system can recognize and respond to nanostructured materials through mechanisms governed by surface characteristics, protein adsorption, particle geometry, and the physicochemical properties of the material. Importantly, immune activation is not necessarily detrimental to regeneration. In fact, a precisely regulated immune response is essential for successful tissue healing. The challenge, therefore, is to understand and control the interaction between nanomaterials and immune cells so that the inflammatory environment is appropriately regulated and subsequently transitions toward tissue remodeling and functional regeneration [13].

The interaction between nanomaterials and stem cells provides another important dimension of the nano–bio interface. Stem-cell fate is regulated by a combination of biochemical, mechanical, topographical, and electrical signals within the cellular microenvironment. Nanostructured materials can reproduce or modulate

several of these cues by providing nanoscale surface architectures, tunable mechanical properties, specific ligand presentation, and controlled cell–material interactions. Such features can influence cell adhesion, cytoskeletal organization, mechanotransduction, proliferation, migration, and lineage-specific differentiation. The ability of nanomaterials to modulate these processes has generated considerable interest in their use as components of engineered microenvironments for bone, cartilage, cardiac, neural, vascular, and skin regeneration [10–13].

Despite these advances, translating promising nanoengineered materials from laboratory research to clinically relevant regenerative applications remains challenging. A major limitation is the incomplete understanding of how nanomaterial properties evolve after exposure to biological systems and how these changes influence long-term biological responses. In addition, differences in experimental models, cell types, biological media, nanomaterial preparation methods, surface functionalization, and characterization protocols make comparisons between studies difficult. Questions concerning biodegradation, persistence, biodistribution, cellular retention, immune recognition, long-term safety, and reproducibility remain important barriers to the rational design and clinical translation of nanoengineered biomaterials [14].

Therefore, a comprehensive understanding of the nano–bio interface requires integration of concepts from nanomaterials science, cell biology, immunology, molecular biology, biomaterials engineering, and regenerative medicine. Rather than considering nanomaterials as passive structural components, increasing evidence suggests that their biological effects arise from dynamic and reciprocal interactions with the surrounding biological environment. Understanding these interactions can provide a rational basis for designing nanomaterials that actively support cellular function, regulate immune responses, and promote tissue regeneration while minimizing undesirable biological effects [12–15].

In this review, we critically examine the fundamental principles governing nano–bio interfaces in regenerative medicine, with particular emphasis on the relationship between nanomaterial physicochemical properties and biological responses. The formation and evolution of the protein corona, cellular recognition and internalization, intracellular trafficking, immune–nanomaterial interactions, stem-cell responses, and the biological fate of nanomaterials are discussed in an integrated framework. We further examine how these interactions influence tissue regeneration across different biological systems and identify current limitations in predicting nano–bio behavior. Finally, emerging strategies for engineering dynamic and biologically adaptive interfaces are discussed, together with major knowledge gaps and future directions required to advance nanoengineered biomaterials from experimental platforms toward clinically meaningful regenerative technologies.

2 | Fundamental Concepts and Determinants of Nano–Bio Interfaces

The biological performance of a nanomaterial is governed by a complex interplay between its intrinsic physicochemical properties and the dynamic biological environment in which it is introduced. At the nanoscale, relatively small changes in particle size, morphology, surface chemistry, charge, roughness, or mechanical characteristics can substantially alter interactions with biomolecules, cell membranes, extracellular matrix components, and immune cells. Accordingly, the nano–bio interface should not be regarded as a simple physical boundary between a nanomaterial and a biological system. Rather, it represents a dynamic and continuously evolving interfacial zone in which molecular adsorption, physicochemical interactions, cellular recognition, and biological signaling occur simultaneously. Understanding the determinants of this interface is therefore essential for predicting nanomaterial behavior and rationally designing nanoengineered systems for regenerative medicine [8–12]. The major physicochemical properties of nanomaterials and their associated biological effects are summarized in *Table 1*.

Table 1. Physicochemical properties governing nano–bio interactions.

Nanomaterial Property	Major Biological Effect	Relevant Biological Process	Potential Regenerative Implication
Particle size	Alters protein adsorption, membrane interaction, and cellular uptake	Cellular recognition and internalization	Controls cellular accessibility and intracellular fate
Shape and morphology	Influences membrane wrapping and cellular interaction	Membrane deformation and endocytosis	Can regulate cell adhesion and intracellular responses
Surface charge	Affects electrostatic interaction with proteins and cell membranes	Protein adsorption and membrane association	Modulates cellular uptake and immune recognition
Surface chemistry	Determines protein binding and receptor interactions	Protein corona formation and cell recognition	Influences cell adhesion and biological signaling
Hydrophobicity	Modifies protein adsorption and membrane interactions	Corona formation and membrane association	Can alter cellular compatibility
Surface roughness	Changes protein adsorption and cell–surface contact	Cell adhesion and mechanotransduction	May influence stem-cell differentiation
Mechanical properties	Regulate cell spreading and cytoskeletal organization	Mechanotransduction	Can direct lineage-specific differentiation
Degradation behavior	Determines persistence and release of degradation products	Intracellular/Extracellular material fate	Controls duration of biological activity

2.1 | Formation of the Nano–Bio Interface

The formation of a nano–bio interface begins immediately when a nanomaterial encounters a biological environment. Physiological fluids contain a complex mixture of proteins, lipids, carbohydrates, ions, nucleic acids, and other biomolecules that can interact with the nanomaterial surface. These interactions are governed by a combination of electrostatic forces, hydrophobic interactions, hydrogen bonding, van der Waals forces, and specific molecular recognition events. Consequently, the physicochemical characteristics initially measured for a nanomaterial under controlled laboratory conditions may not accurately represent the surface that cells subsequently encounter [9].

The biological environment also determines the temporal evolution of the interface. Biomolecules may rapidly adsorb onto the nanomaterial surface, undergo conformational changes, dissociate, or be replaced by other molecules with greater surface affinity. This continuous exchange creates a dynamic interfacial environment rather than a stable coating. The resulting interface can alter the effective size, surface charge, hydrophobicity, aggregation behavior, and biological recognition of the nanomaterial. Therefore, characterization of nanomaterials exclusively before biological exposure may provide an incomplete description of their functional properties [16].

The nano–bio interface is additionally influenced by the local tissue microenvironment. Factors such as pH, ionic strength, extracellular matrix composition, oxygen concentration, inflammatory mediators, and enzymatic activity can differ considerably between healthy, injured, and regenerating tissues. Such variations may modify nanomaterial stability and surface interactions, thereby affecting cellular responses. In regenerative medicine, this dynamic behavior is particularly relevant because the biological environment changes substantially during the progression from acute inflammation to tissue formation and remodeling [10–14].

2.2 | Influence of Nanomaterial Size and Shape

Particle size is one of the most important determinants of nano–bio interactions. Changes in nanoscale dimensions can affect surface area, protein adsorption, cellular uptake, tissue penetration, intracellular trafficking, and clearance. Smaller nanomaterials generally possess higher specific surface areas and may

exhibit increased interactions with biological molecules. However, the relationship between size and biological response is not necessarily linear because surface chemistry, aggregation state, morphology, and the biological environment can substantially modify the apparent effects of particle size.

Nanomaterial size also influences interactions with cell membranes. The probability and mechanism of cellular internalization can vary depending on particle dimensions and the energetic requirements associated with membrane wrapping. Once internalized, particle size can further influence intracellular trafficking and localization. These effects become particularly important when nanomaterials are designed to modulate cellular behavior in regenerative microenvironments [17].

Particle shape is another critical determinant that is sometimes overlooked in comparison with size. Spherical, rod-like, tubular, disk-shaped, fiber-like, and irregular nanostructures can exhibit distinct interactions with cells and biological molecules. Shape can influence membrane contact area, orientation at the cell surface, cellular uptake pathways, intracellular trafficking, and interactions with phagocytic cells. In addition, anisotropic nanostructures may exhibit directional interactions with extracellular matrix components and cell membranes that cannot be predicted solely from their equivalent spherical diameter [18].

Importantly, size and shape should not be considered independent variables. A change in morphology can simultaneously alter surface area, curvature, aspect ratio, aggregation tendency, and cellular interaction patterns. Consequently, systematic evaluation of nanomaterial geometry is required when attempting to establish structure–biological response relationships.

2.3 | Surface Chemistry and Surface Charge

The chemical composition of a nanomaterial surface directly determines its interaction with the surrounding biological environment. Functional groups exposed at the surface can participate in hydrogen bonding, electrostatic interactions, hydrophobic interactions, and specific receptor-mediated recognition. Surface functionalization can therefore be used to modify the biological identity of nanomaterials and regulate their interactions with proteins, extracellular matrix molecules, and cell membranes.

Surface charge is particularly important because cell membranes and many extracellular biomolecules possess net negative charges under physiological conditions. Positively charged nanomaterials may exhibit strong electrostatic interactions with negatively charged cellular membranes, potentially increasing membrane association and cellular internalization. However, excessive positive surface charge can also disrupt membrane integrity, increase nonspecific protein adsorption, and induce cellular stress or inflammatory responses. Neutral or weakly charged surfaces may reduce nonspecific interactions, although they can also modify cellular recognition and uptake.

The biological consequences of surface charge depend strongly on the surrounding medium. Adsorption of biomolecules can partially shield the original surface charge and modify the effective electrostatic properties perceived by cells. In addition, ionic strength and pH can influence charge distribution and colloidal stability. Therefore, zeta potential measurements obtained in simplified aqueous systems should be interpreted cautiously when predicting behavior under physiological conditions [19].

Surface chemistry also provides opportunities to engineer nanomaterials with biologically instructive properties. By controlling the density and spatial organization of functional groups, it may be possible to regulate cell adhesion, extracellular matrix interactions, immune recognition, and stem-cell behavior. In regenerative medicine, such control can be particularly valuable for designing interfaces that promote desirable cellular responses while minimizing nonspecific or inflammatory interactions.

2.4 | Surface Roughness and Topographical Features

Beyond chemical composition, nanoscale surface topography plays an important role in determining how cells interact with engineered materials. Cells continuously sense the physical characteristics of their surrounding environment through membrane receptors, focal adhesions, cytoskeletal structures, and

mechanosensitive signaling pathways. Consequently, nanoscale variations in surface roughness, curvature, patterning, and spatial organization can influence cell adhesion and downstream cellular behavior [20]. As illustrated in *Fig. 1*, these topographical cues are sensed through membrane receptors, focal adhesions, cytoskeletal structures, and mechanosensitive signaling pathways, ultimately influencing cellular behavior.

Nanostructured surfaces can provide topographical cues that partially reproduce features of the native extracellular matrix. Such cues may alter the organization of adhesion proteins, cytoskeletal architecture, focal adhesion maturation, and intracellular signaling. These changes can subsequently affect cell spreading, migration, proliferation, and differentiation. In stem-cell-based regenerative strategies, nanoscale topography may therefore contribute to the regulation of lineage commitment by modifying the mechanical and physical signals perceived by cells.

Surface roughness can also influence the adsorption and organization of biomolecules at the interface. Increased surface complexity may provide additional binding sites and alter the spatial distribution of adsorbed proteins and extracellular matrix components. However, the biological effects of roughness cannot be separated completely from other surface properties, because changes in topography may simultaneously modify surface area, wettability, protein adsorption, and mechanical interactions.

The relationship between surface topography and biological response is consequently highly context-dependent. A topographical feature that promotes adhesion in one cell type may have limited or even opposite effects in another. Rational design therefore requires consideration of both the physical scale of surface features and the specific biological function that the engineered interface is intended to support [20–22].

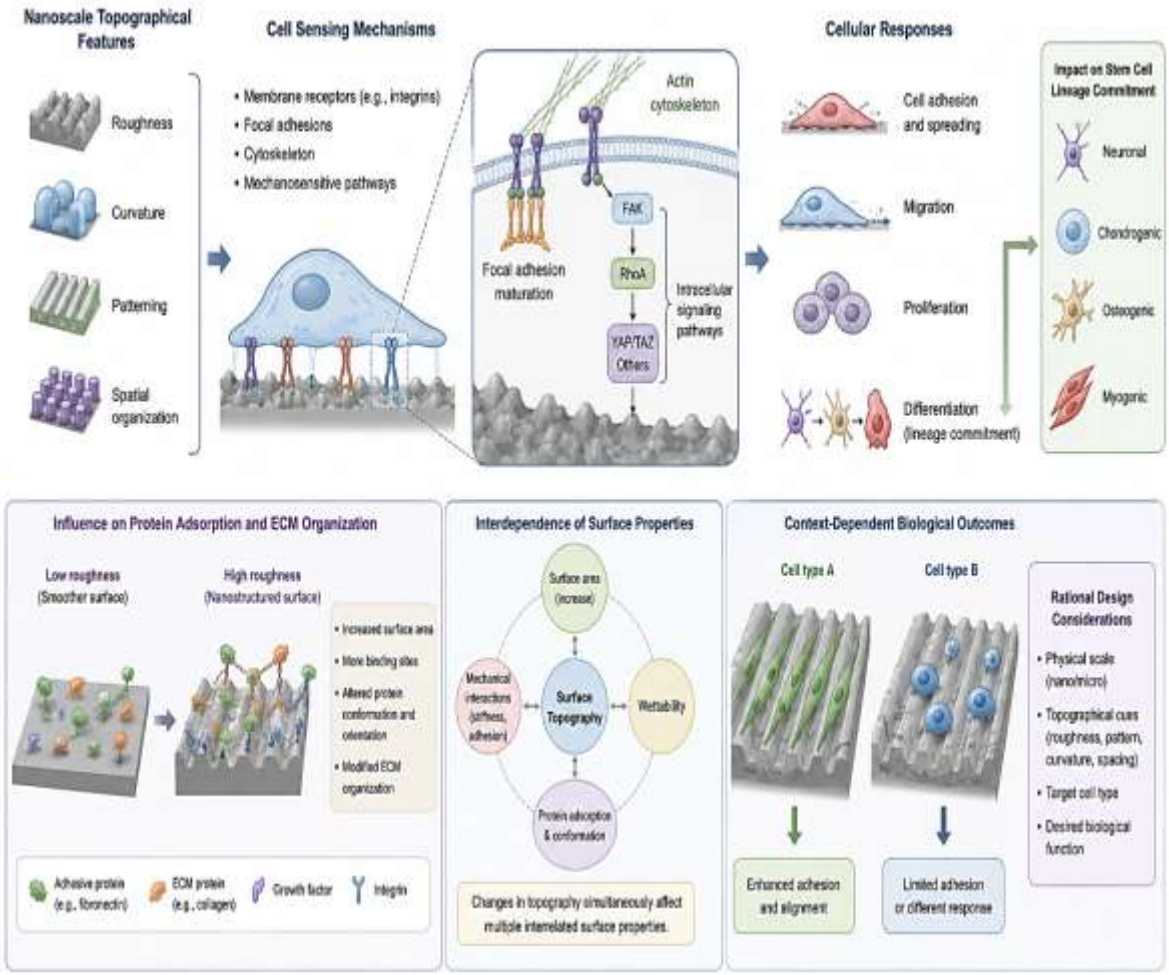

Fig 1. Schematic illustration of how nanoscale surface topography regulates cellular interactions, protein adsorption, and cell fate through topographical and mechanobiological cues.

2.5 | Mechanical and Interfacial Properties

Mechanical properties represent another important component of the nano–bio interface, particularly in tissue regeneration, where cells continuously respond to the mechanical characteristics of their microenvironment. Parameters such as stiffness, elasticity, viscoelasticity, deformability, and interfacial adhesion can influence cell behavior through mechanotransduction pathways. Cells detect mechanical signals through integrins, focal adhesions, the actin cytoskeleton, and mechanosensitive ion channels, ultimately translating extracellular mechanical information into intracellular biochemical signals [20].

The mechanical compatibility between a nanomaterial and its surrounding tissue can influence cellular attachment, deformation, migration, and differentiation. For example, cells residing in tissues with distinct mechanical properties may respond differently to the same nanomaterial. Bone, cartilage, neural tissue, and soft connective tissues differ substantially in stiffness and viscoelastic behavior, suggesting that a universal mechanical design for nanoengineered biomaterials is unlikely to be optimal across all regenerative applications.

At the nanoscale, interfacial mechanical properties can also differ from the bulk properties of a material. Surface layers, adsorbed biomolecules, hydration shells, and molecular interactions may collectively determine the mechanical environment experienced by cells. This distinction is important because cells interact primarily with the material surface rather than its bulk interior. Therefore, characterization of nanoengineered biomaterials should ideally incorporate both bulk mechanical properties and surface-associated mechanical behavior.

The combination of mechanical and biochemical cues can further generate synergistic effects. Changes in substrate stiffness may alter receptor clustering and cytoskeletal tension, while surface chemistry and topography can modify the strength and organization of cell adhesion. Understanding these coupled effects is essential for developing biomaterials capable of providing physiologically relevant signals to regenerating tissues [23].

2.6 | Dynamic Nature of the Nano–Bio Interface

One of the defining characteristics of the nano–bio interface is its dynamic nature. Unlike conventional material surfaces, which are characterized under static conditions, nanomaterial interfaces continuously evolve after exposure to biological systems. Changes in biomolecular adsorption, particle aggregation, degradation, surface restructuring, enzymatic modification, and cellular interaction can progressively alter the properties of the interface.

This dynamic behavior becomes particularly important in regenerative medicine because tissue repair itself is a temporally regulated process. The biological environment evolves from an initial inflammatory phase toward tissue formation and subsequent remodeling. During these stages, the composition of extracellular proteins, immune-cell populations, extracellular matrix components, pH, enzymatic activity, and mechanical properties can change considerably. A nanomaterial that interacts favorably with cells during one stage of regeneration may therefore behave differently at a later stage.

Nanomaterial degradation represents another important mechanism contributing to interface evolution. As materials undergo hydrolysis, enzymatic degradation, dissolution, oxidation, or structural disintegration, new surfaces may become exposed and previously inaccessible components may enter the biological environment. These changes can modify cellular recognition and immune responses over time. For biodegradable nanoengineered materials, biological fate should consequently be considered as a continuous process rather than a single endpoint.

The dynamic nature of the nano–bio interface also highlights the limitations of conventional characterization approaches. Measurements performed before biological exposure or at a single time point may fail to capture the evolving properties that ultimately determine biological performance. Integrating time-resolved

physicochemical characterization with longitudinal biological assessment may therefore provide a more accurate understanding of nanomaterial behavior [20–23].

Taken together, the formation and evolution of the nano–bio interface are governed by multiple interconnected physicochemical parameters rather than by any single material property. Size, shape, surface chemistry, charge, topography, mechanical behavior, and degradation characteristics collectively determine how nanomaterials interact with biological systems. Importantly, these properties can be substantially modified after exposure to physiological environments. This recognition provides the foundation for understanding the next level of nano–bio interactions: the formation of a dynamic biomolecular layer on the nanomaterial surface and its role in defining the biological identity of the material. The formation, composition, and functional consequences of this protein corona are discussed in the following section.

3 | Protein Corona and the Biological Identity of Nanomaterials

When nanomaterials enter a biological environment, their original physicochemical properties are rapidly modified through interactions with surrounding biomolecules. Among these interactions, protein adsorption is particularly important because it generates a biomolecular layer known as the protein corona. This corona can alter the apparent surface properties, cellular recognition, biological fate, and interactions of nanomaterials with tissues. Consequently, cells often interact not with the pristine nanomaterial, but with a dynamically transformed biological interface [22]. The key determinants of protein corona formation and its major biological consequences are summarized in *Table 2*.

3.1 | Formation and Evolution of the Protein Corona

Protein corona formation begins rapidly after exposure to biological fluids, as proteins compete for available surface sites according to their concentration, affinity, and binding kinetics. Highly abundant proteins may initially dominate the surface, whereas proteins with stronger affinity can progressively replace them. Protein adsorption may also alter protein conformation and expose molecular domains that influence subsequent biological recognition [23].

The composition of the corona depends strongly on the biological environment. Plasma, extracellular matrix-rich environments, and cell-conditioned media can generate different corona profiles on the same nanomaterial. In addition, corona formation can modify hydrodynamic size, surface charge, aggregation, and colloidal stability, meaning that the properties of nanomaterials in physiological environments may differ substantially from those measured in simple aqueous systems.

3.2 | Hard and Soft Protein Corona

The protein corona is commonly described as comprising hard and soft components. The hard corona contains relatively strongly bound proteins that remain associated with the nanomaterial for longer periods, whereas the soft corona consists of more weakly and dynamically associated proteins. This distinction is useful for understanding the temporal evolution of the nano–bio interface, although protein adsorption exists along a continuous range of binding affinities rather than as two completely separate populations [21].

3.3 | Factors Governing Protein Corona Composition

Corona composition is determined by both nanomaterial properties and the surrounding biological environment. Surface charge, hydrophobicity, surface chemistry, functional groups, curvature, roughness, and particle size can influence protein adsorption. At the same time, protein abundance, concentration, molecular properties, pH, temperature, ionic strength, and extracellular matrix composition affect the resulting corona. Therefore, the protein corona should not be regarded as an intrinsic property of a nanomaterial. Instead, it represents a dynamic interface between the material and its biological context, which is particularly important for reproducibility and the interpretation of biological experiments [23].

3.4 | Protein Corona and Cellular and Immune Recognition

The protein corona acts as a molecular interface between nanomaterials and cells. Adsorbed proteins can interact with cell-surface receptors, influence membrane association, and modify endocytic pathways. Consequently, differences in cellular uptake may result from differences in the biological interface rather than from differences in the nominal composition of the nanomaterials.

The corona also influences immune recognition. Adsorption of specific proteins may promote opsonization and uptake by macrophages or other phagocytic cells, whereas other proteins may reduce or modify immune recognition. In regenerative medicine, this interaction is particularly important because controlled immune activation can support tissue repair, while excessive or persistent inflammation may impair regeneration and promote fibrosis [24].

3.5 | Protein Corona-Mediated Cellular Uptake

Once formed, the protein corona can determine how efficiently nanomaterials are internalized and which cellular pathways are involved. Uptake may occur through clathrin-mediated endocytosis, caveolae-associated pathways, macropinocytosis, or phagocytosis, depending on particle properties and cell type.

Importantly, greater cellular uptake does not necessarily indicate better biological performance. Excessive internalization may result in intracellular accumulation and cellular stress, whereas limited uptake may be desirable for materials intended to provide extracellular structural or mechanical cues. Thus, the optimal degree of uptake depends on the intended biological function of the nanomaterial [21].

3.6 | Dynamic Protein Corona in Regenerative Microenvironments

Regenerating tissues undergo continuous changes in protein composition, extracellular matrix organization, inflammatory signaling, and cellular populations. Consequently, the protein corona may evolve throughout different stages of tissue repair.

This dynamic behavior suggests that a nanomaterial may acquire different biological identities over time. Rather than considering the corona as a static coating, it can be viewed as a dynamic molecular fingerprint that changes according to tissue location, biological state, and stage of regeneration [24].

3.7 | Implications for Regenerative Nanomaterials

Understanding protein corona formation provides an important basis for designing nanomaterials with more predictable biological behavior. Surface charge, hydrophilicity, functional groups, particle size, morphology, and surface architecture can be engineered to influence protein adsorption and subsequent cellular interactions.

The goal is not necessarily to prevent protein adsorption but to create a favorable biological interface capable of supporting cell adhesion, regulating immune responses, and promoting tissue regeneration. However, predicting corona formation under clinically relevant conditions remains challenging because regenerative tissues contain complex and continuously changing molecular environments [24].

Table 2. Protein Corona: Formation, determinants, and biological consequences.

Aspect	Key Determinants	Biological Consequence	Relevance to Regeneration
Corona formation	Surface chemistry, charge, size, shape, protein concentration	Establishment of a new biological identity	Determines subsequent cell–material interactions
Hard corona	Strong protein–surface interactions	Relatively stable biomolecular layer	Influences persistent cellular recognition
Soft corona	Weak and dynamic protein interactions	Rapid exchange of adsorbed proteins	Contributes to dynamic biological behavior
Protein conformation	Surface chemistry and binding strength	Exposure or masking of functional domains	Can modify receptor-mediated cellular responses

Table 2. Continued.

Aspect	Key Determinants	Biological Consequence	Relevance to Regeneration
Biological environment	Plasma, ECM, interstitial fluid, tissue state	Tissue-specific corona composition	May produce different biological responses in different tissues
Opsonization	Adsorption of immunoglobulins and complement-related proteins	Enhanced immune recognition and clearance	Can influence inflammatory responses
Corona-mediated uptake	Corona composition and cell type	Changes endocytic pathway and uptake efficiency	Determines intracellular exposure
Dynamic corona	Time, tissue microenvironment, cellular interactions	Continuous evolution of biological identity	May influence different stages of tissue regeneration

4 | Cellular Recognition, Uptake, and Intracellular Fate of Nanomaterials

Following the formation of the nano–bio interface and protein corona, nanomaterials interact with cellular membranes and intracellular components. These interactions determine whether nanomaterials remain extracellular, become internalized, undergo intracellular degradation, or influence cellular signaling. Their biological effects depend on physicochemical properties, corona composition, cell type, and the surrounding tissue microenvironment. Understanding these processes is essential for determining how nanomaterials influence proliferation, differentiation, metabolism, inflammation, and tissue regeneration [25]. The major cellular responses and intracellular processes associated with nanomaterial exposure are summarized in *Table 3*. Importantly, cellular interaction does not necessarily imply cellular uptake. Depending on their characteristics and intended application, nanomaterials may remain associated with the extracellular matrix, interact transiently with cell membranes, or enter cells through specific endocytic pathways. Each route can generate distinct biological outcomes.

4.1 | Cell Membrane–Nanomaterial Interactions

The cell membrane is the first cellular barrier encountered by nanomaterials and contains phospholipids, membrane proteins, glycoproteins, and cholesterol that regulate interactions with external materials. Electrostatic forces, hydrophobic interactions, van der Waals forces, and receptor-mediated mechanisms can determine whether a nanomaterial remains at the membrane or becomes internalized. Particle size, shape, surface charge, hydrophobicity, and functionalization strongly influence membrane interactions. However, the protein corona formed in biological fluids can modify the effective surface presented to cells and consequently alter cellular recognition. Nanomaterial–membrane interactions may also induce membrane deformation and cytoskeletal changes. While controlled interactions can facilitate cellular signaling and internalization, excessive membrane interaction may disrupt membrane integrity and cellular homeostasis. Therefore, appropriate control of surface properties is essential for regenerative applications [26].

4.2 | Cellular Internalization and Intracellular Trafficking

Nanomaterials can enter cells through several pathways, including clathrin-mediated endocytosis, caveolae-associated uptake, macropinocytosis, and phagocytosis. The dominant pathway depends on particle characteristics and cell identity. Phagocytic cells, particularly macrophages, are especially important because they efficiently recognize and internalize particulate materials.

Following internalization, nanomaterials are commonly transported through endosomal compartments and may subsequently reach lysosomes. Their intracellular fate depends on size, morphology, surface chemistry, and degradation characteristics. Some materials remain within vesicular compartments, whereas others may interact with the cytoplasm or intracellular organelles. Intracellular localization is therefore more important than uptake alone. A nanomaterial that remains within lysosomes may have a substantially different biological effect from one capable of interacting with mitochondria or other intracellular structures [27].

4.3 | Interactions with Intracellular Organelles

After internalization, nanomaterials may interact with lysosomes, mitochondria, endoplasmic reticulum, and, in some cases, the nucleus. Mitochondrial interactions are particularly relevant because mitochondria regulate cellular energy production and redox balance. Nanomaterials may alter mitochondrial function and ROS production, potentially influencing cellular metabolism and stress responses. Lysosomes represent another major site of nanomaterial accumulation and degradation. Persistent materials may affect lysosomal function or autophagic activity, whereas biodegradable systems may gradually undergo intracellular degradation. These interactions can modify cellular signaling, metabolism, and survival. Consequently, intracellular localization and degradation should be considered important parameters when evaluating the biological performance of nanomaterials [26].

4.4 | Oxidative Stress and Cellular Responses

Nanomaterials can modulate ROS production through mitochondrial interactions, membrane perturbation, catalytic activity, inflammatory signaling, and degradation processes. ROS are not inherently detrimental because controlled redox signaling participates in proliferation, differentiation, and cellular adaptation. However, excessive or persistent ROS generation can lead to oxidative stress, mitochondrial dysfunction, macromolecular damage, and impaired cellular function. The outcome depends on nanomaterial concentration, exposure duration, surface properties, and cell type. Nanomaterials may also influence autophagy and apoptosis. Autophagy can initially act as a protective mechanism by removing damaged cellular components, whereas severe or prolonged stress may activate apoptotic pathways. In regenerative medicine, maintaining an appropriate balance between cellular stimulation and stress is therefore critical [24].

4.5 | Cell-Type-Specific Responses

The biological response to nanomaterials varies considerably among different cell types. Stem cells, endothelial cells, fibroblasts, neurons, osteoblasts, and immune cells differ in membrane composition, receptor expression, endocytic activity, metabolism, and intracellular processing. For stem cells, nanomaterial interactions may influence self-renewal, differentiation, and metabolic activity. Endothelial cells may respond through changes in adhesion, cytoskeletal organization, and oxidative signaling, whereas fibroblasts may alter extracellular matrix production and remodeling. Immune cells exhibit particularly important responses because their recognition and processing of nanomaterials can influence inflammatory signaling and tissue repair. This cell-type specificity emphasizes the importance of evaluating nanomaterials using physiologically relevant models rather than relying exclusively on a single cell line [28].

4.6 | Implications for Regenerative Medicine

The cellular fate of nanomaterials directly influences their regenerative function. Depending on their design, nanomaterials may act primarily as extracellular structural cues, regulators of cell adhesion and mechanotransduction, or intracellular modulators of cellular signaling.

For extracellular applications, excessive cellular uptake may be unnecessary, whereas intracellularly active systems require controlled internalization and appropriate intracellular localization. Similarly, biodegradable nanomaterials can be designed to provide temporary biological signals before gradually disappearing during tissue regeneration.

Therefore, successful nano–bio interface design requires establishing relationships between material properties, cellular uptake, intracellular fate, and regenerative outcomes. Evaluation should extend beyond simple cell viability and include cellular uptake, intracellular localization, oxidative balance, mitochondrial function, inflammatory signaling, and long-term cellular behavior.

Cellular recognition, uptake, and intracellular fate represent critical determinants of nanomaterial cell interactions. These processes determine whether nanomaterials function as beneficial biological cues,

relatively inert structural components, or sources of cellular stress. Because immune cells are also major regulators of these processes, the next section focuses on nanomaterial immune system interactions and their role in tissue regeneration [27].

Table 3. Cellular responses to Nanomaterials and their regenerative implications.

Cellular Event	Main Mechanism	Possible Beneficial Response	Potential Adverse Response
Membrane interaction	Electrostatic, hydrophobic, and receptor-mediated interactions	Cell adhesion and signaling	Membrane disruption
Cellular uptake	Endocytosis, macropinocytosis, phagocytosis	Intracellular biological modulation	Excessive accumulation
Endosomal trafficking	Vesicular transport and maturation	Controlled intracellular processing	Endosomal/Lysosomal stress
Lysosomal interaction	Acidic degradation and enzymatic processing	Material degradation	Lysosomal dysfunction
Mitochondrial interaction	Changes in mitochondrial signaling and metabolism	Metabolic adaptation	Mitochondrial dysfunction
ROS modulation	Redox signaling	Controlled cellular signaling and adaptation	Oxidative stress
Autophagy	Removal of damaged cellular components	Cellular homeostasis	Dysregulated autophagy
Apoptosis	Activation of programmed cell-death pathways	Removal of severely damaged cells	Reduced cell survival
Cytoskeletal remodeling	Actin organization and focal adhesion signaling	Mechanotransduction and differentiation	Abnormal cell morphology
Gene regulation	Intracellular signaling and transcriptional regulation	Lineage-specific differentiation	Altered cellular phenotype

5 | Nano–Immune System Interactions

The immune system represents one of the most important biological determinants of nanomaterial behavior following exposure to injured or regenerating tissues. Unlike inert synthetic systems, living tissues actively recognize and respond to foreign materials through coordinated innate and adaptive immune mechanisms. Nanomaterials can therefore influence tissue regeneration not only through direct interactions with resident cells but also by modulating the inflammatory and immunological microenvironment. The outcome of these interactions depends on nanomaterial physicochemical properties, surface characteristics, protein corona composition, degradation behavior, and the physiological state of the surrounding tissue [21].

Historically, immune responses to biomaterials were often considered primarily in the context of adverse inflammation, foreign-body reactions, and material rejection. However, increasing evidence indicates that immune activity is an integral component of successful tissue regeneration. The initial inflammatory response can remove damaged tissue, recruit progenitor cells, stimulate vascularization, and initiate subsequent remodeling processes. The critical challenge is therefore not complete suppression of immune recognition but rather the development of nanoengineered interfaces capable of regulating the magnitude, duration, and phenotype of immune responses in a manner compatible with tissue repair [22]. As shown in *Fig. 2*, nanomaterial properties shape innate and adaptive immune responses that ultimately determine regenerative versus fibrotic outcomes.

5.1 | Innate Immune Recognition of Nanomaterials

Innate immunity provides the first line of biological recognition following exposure to nanomaterials. Components of the innate immune system, including macrophages, neutrophils, dendritic cells, natural killer cells, and the complement system, can recognize molecular and structural features associated with foreign materials.

The recognition process may occur directly through interactions between cell-surface receptors and nanomaterial-associated structures or indirectly through proteins adsorbed onto the material surface. Pattern-recognition receptors and other immune-associated receptors can respond to changes in the local molecular

environment, potentially initiating intracellular signaling cascades and cytokine production. The extent of innate immune activation depends strongly on material properties. Particle size, surface charge, morphology, hydrophobicity, aggregation state, and surface functionalization can influence interactions with immune cells. Smaller particles may exhibit distinct biodistribution and cellular uptake characteristics compared with larger structures, whereas highly charged or reactive surfaces may promote stronger immune interactions [29].

However, no single physicochemical parameter is sufficient to predict immune behavior. Rather, immune recognition emerges from the combined effects of material characteristics and the biological interface established after exposure to physiological fluids.

5.2 | Complement Activation and Opsonization

The complement system represents an important component of innate immune recognition and can influence the biological fate of nanomaterials. Complement proteins may interact with nanomaterial-associated surfaces and initiate a cascade of proteolytic reactions that contribute to opsonization, immune-cell recruitment, and inflammatory signaling. Opsonization can facilitate recognition and uptake by phagocytic cells. In this context, complement activation may influence the extent to which nanomaterials are retained within tissue, internalized by macrophages, or transported through biological compartments. The magnitude of complement activation depends on multiple characteristics of the nanomaterial, including surface chemistry, charge, size, morphology, and the composition of the associated biomolecular layer. Surface-associated proteins can either promote or reduce complement recognition depending on their abundance, orientation, and functional state. In regenerative medicine, controlled complement activation may participate in the early inflammatory response required for tissue repair. However, excessive or persistent complement activation may contribute to prolonged inflammation and tissue damage. Consequently, understanding and controlling complement–nanomaterial interactions represent an important consideration in the development of clinically compatible nanoengineered biomaterials [30].

5.3 | Macrophage–Nanomaterial Interactions

Macrophages are among the most important cellular mediators of the interaction between biomaterials and the immune system. They participate in the recognition and removal of foreign materials, the secretion of inflammatory mediators, recruitment of other immune cells, extracellular matrix remodeling, and coordination of tissue repair.

Following exposure to nanomaterials, macrophages may internalize particles through phagocytosis or other endocytic mechanisms. The subsequent response depends on particle characteristics, intracellular localization, degradation behavior, and the surrounding inflammatory environment. Nanomaterials can influence macrophage metabolism, cytoskeletal organization, cytokine secretion, oxidative signaling, and cellular phenotype.

Macrophage responses are often described using the simplified M1/M2 framework, in which M1-like states are associated predominantly with pro-inflammatory functions, and M2-like states with tissue repair and remodeling. Although this classification is useful conceptually, macrophage activation in vivo is considerably more heterogeneous and dynamic. Macrophages can adopt a continuum of functional states in response to combinations of biochemical, mechanical, metabolic, and environmental signals.

Nanoengineered materials can influence this functional spectrum by modifying the local microenvironment. Surface chemistry, topography, stiffness, degradation products, and nanoscale architecture may all contribute to macrophage behavior. Materials designed to support regeneration may therefore be engineered to promote a transition from an early inflammatory state toward a reparative phenotype as tissue healing progresses [31].

5.4 | Macrophage Polarization and Tissue Regeneration

The temporal regulation of macrophage activity is particularly important for successful tissue repair. Following tissue injury, an early inflammatory response is generally necessary to remove damaged cells and

extracellular debris and to initiate repair-associated signaling. As regeneration progresses, prolonged inflammatory activity can become detrimental and interfere with matrix deposition, vascularization, and tissue maturation. Nanoengineered biomaterials may influence this transition by providing specific physical and biochemical signals. Nanoscale topography can affect macrophage adhesion and cytoskeletal organization, while surface chemistry and material degradation can alter intracellular signaling and cytokine production. In addition, nanomaterials may modify the local mechanical environment and influence mechanosensitive pathways involved in immune-cell activation. The ability to regulate macrophage behavior is therefore increasingly considered a central design principle in regenerative biomaterials. Rather than developing materials that simply avoid immune recognition, researchers are investigating immunomodulatory interfaces capable of guiding immune responses toward regenerative outcomes. This approach is particularly relevant to tissues in which chronic inflammation strongly compromises regeneration. In such environments, controlling macrophage activity may influence downstream processes including fibroblast activation, extracellular matrix organization, angiogenesis, and stem-cell recruitment [32].

5.5 | Neutrophils and Early Inflammatory Responses

Neutrophils are among the earliest immune cells recruited to sites of tissue injury. They contribute to the removal of cellular debris and microorganisms and release a range of enzymes, reactive species, cytokines, and extracellular structures that shape the inflammatory microenvironment. Nanomaterials can influence neutrophil recruitment and activation through direct surface interactions and indirect modulation of inflammatory signaling. Excessive activation may increase oxidative and proteolytic stress within the tissue, whereas controlled neutrophil activity can contribute to effective early-stage tissue repair. The role of neutrophils in regenerative nanomedicine has historically received less attention than macrophage responses. However, increasing understanding of the temporal coordination between neutrophils and macrophages suggests that neutrophil behavior may influence subsequent macrophage recruitment and functional polarization. This interaction emphasizes the importance of considering immune responses as interconnected networks rather than isolated cellular events. A nanomaterial that modifies neutrophil activity may consequently influence downstream macrophage behavior and the broader regenerative trajectory [33].

5.6 | Dendritic Cells and Adaptive Immune Responses

Dendritic cells serve as important links between innate and adaptive immunity. Their ability to process and present antigens allows them to influence T-cell activation and the development of longer-term immune responses. Nanomaterials can interact with dendritic cells through uptake, surface receptor engagement, and modulation of intracellular signaling. Depending on material properties and biological context, these interactions may influence dendritic-cell maturation, antigen presentation, and cytokine secretion. Although adaptive immune responses are generally less dominant during the earliest stages of biomaterial implantation than innate mechanisms, their potential contribution to long-term material compatibility should not be overlooked. Persistent or poorly degradable nanomaterials may remain associated with immune cells for extended periods and potentially influence chronic immune surveillance. Understanding these processes is particularly relevant when designing long-lasting regenerative scaffolds or nanostructured materials intended to remain within tissues for prolonged periods [32].

5.7 | Nanomaterials, Inflammation, and Cytokine Signaling

Inflammation is a complex network of cellular and molecular interactions rather than a single biological response. Nanomaterials can influence this network through changes in cytokine secretion, chemokine signaling, oxidative balance, inflammasome activation, and cell–cell communication. The magnitude and duration of inflammatory signaling are critical determinants of regenerative outcome. A transient inflammatory response can support tissue repair by recruiting immune and progenitor cells, whereas persistent inflammatory signaling may promote fibrosis, extracellular matrix dysregulation, and impaired tissue maturation. Nanomaterials may modify inflammatory signaling through several mechanisms. Cellular

internalization can alter intracellular stress pathways, while surface-associated proteins can influence receptor-mediated signaling. Degradation products may additionally modify local pH, ionic composition, or metabolic conditions. The relationship between nanomaterials and inflammation is therefore highly context-dependent. The same material may produce different inflammatory outcomes depending on particle concentration, tissue type, implantation site, degradation rate, and the pre-existing inflammatory state of the host [31].

5.8 | Inflammasome Activation

Inflammasomes are intracellular multiprotein complexes that detect cellular stress and danger-associated signals and regulate the maturation of inflammatory mediators. Certain nanomaterials have been reported to influence inflammasome-associated signaling through mechanisms involving lysosomal stress, ROS, ion imbalance, and particulate recognition. Inflammasome activation may contribute to the production of inflammatory cytokines and can influence macrophage and other immune-cell behavior. In the context of regenerative medicine, excessive activation may interfere with tissue repair, whereas appropriately regulated inflammatory signaling may participate in normal wound healing. The potential for inflammasome activation highlights the importance of assessing intracellular mechanisms rather than relying exclusively on gross measures of inflammation. Understanding how nanomaterial characteristics influence lysosomal integrity, oxidative signaling, and intracellular danger responses may provide valuable insights into their immunological behavior [34].

5.9 | Adaptive Immunity and Long-Term Immune Interactions

Although innate immune mechanisms dominate many early responses to nanomaterials, adaptive immunity can become relevant during prolonged exposure. Persistent materials or repeated exposure may alter antigen presentation and influence T-cell responses. T cells can contribute to chronic inflammatory processes, tissue remodeling, and immune regulation. Their interactions with biomaterials may be mediated indirectly through antigen-presenting cells and the cytokine environment rather than through direct recognition of the material itself. The long-term immunological consequences of nanomaterials remain insufficiently characterized for many regenerative applications. This issue is particularly important for materials designed to remain in tissues over extended periods. Long-term studies should therefore examine not only local inflammation but also systemic immune responses, material persistence, degradation, and changes in immune-cell populations [35].

5.10 | Immunomodulatory Design of Nano–Bio Interfaces

The emerging concept of immunomodulatory biomaterials represents a shift from passive biocompatibility toward active regulation of immune responses. In this framework, nanomaterials are designed to interact with immune cells in a controlled manner and to create a microenvironment that supports the progression from inflammation toward tissue repair. Several material characteristics can contribute to this process. Surface topography may alter macrophage morphology and adhesion, while mechanical properties can influence immune-cell mechanosensing. Surface chemistry can regulate protein adsorption and receptor interactions, and degradation characteristics can determine the duration and intensity of material-associated signals. The spatial and temporal presentation of these cues is equally important. A material that provides a single static signal may be less effective than one capable of adapting to changes in the regenerative microenvironment. Future nanoengineered systems may therefore incorporate dynamic interfaces that evolve during tissue healing.

Such approaches could enable materials to support early immune-mediated clearance and tissue preparation while subsequently promoting anti-inflammatory and regenerative processes. This concept represents an important bridge between nanomaterial engineering and the biological complexity of tissue repair [30].

5.11 | Nano–Immune Interactions as Determinants of Regenerative Outcomes

The biological effects of nanomaterials ultimately emerge from the interaction between material properties, immune responses, resident cells, and the extracellular matrix. Immune cells do not function independently;

rather, they communicate with stem cells, endothelial cells, fibroblasts, and other tissue-resident populations through cytokines, chemokines, extracellular vesicles, and direct cell–cell interactions. Consequently, modulation of immune responses by nanomaterials can produce secondary effects throughout the regenerative microenvironment. For example, changes in macrophage activity may influence stem-cell recruitment and differentiation, angiogenesis, extracellular matrix deposition, and tissue remodeling. Similarly, altered neutrophil or dendritic-cell activity may affect subsequent immune-cell recruitment and the duration of inflammation.

This interconnected nature of the regenerative response suggests that the immunological behavior of a nanomaterial should be considered a central component of its overall biological identity rather than an isolated safety parameter [26].

5.12 | Challenges and Future Directions

Despite substantial progress, several challenges remain in understanding nano–immune interactions. The diversity of nanomaterial compositions, surface structures, experimental conditions, and biological models makes direct comparison between studies difficult. In addition, simplified cell-culture systems may not adequately reproduce the spatial and temporal complexity of immune responses within regenerating tissues. Future studies should therefore integrate multiple biological scales, ranging from molecular interactions and intracellular signaling to multicellular tissue responses. Advanced three-dimensional culture models, organoid systems, organ-on-chip platforms, spatial omics, single-cell analysis, and longitudinal imaging may provide more realistic approaches for investigating nano–immune interactions. An additional priority is the development of predictive relationships between material properties and immune outcomes. Such relationships could facilitate rational design rather than empirical optimization. Combining high-throughput nanomaterial screening with computational modeling and mechanistic biological analysis may ultimately enable the identification of material characteristics associated with specific regenerative immune responses. Interactions between nanomaterials and the immune system represent a decisive component of regenerative nanomedicine. The objective is shifting from simply minimizing immune recognition toward actively controlling immune–material interactions to create a regenerative microenvironment. Understanding how nanomaterials influence macrophages, neutrophils, dendritic cells, complement activation, inflammatory signaling, and longer-term immune responses provides a foundation for designing materials that actively participate in tissue repair. The next section will build on this concept by examining how nanoengineered interfaces influence stem-cell behavior, fate determination, and regenerative potential [26], [27], [29–32].

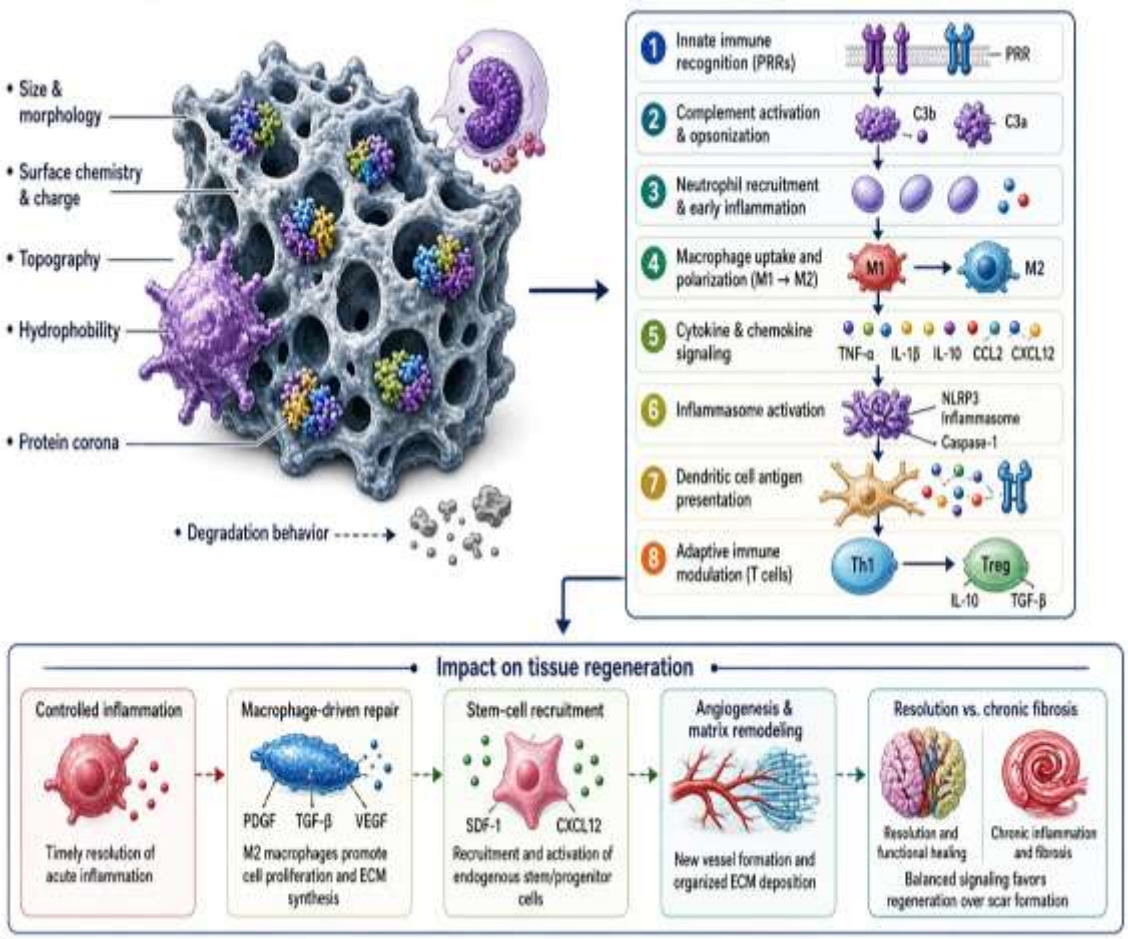

Fig. 2. Sequential nano–immune interactions and their impact on the balance between inflammation and tissue regeneration.

6 | Nanomaterials and Stem-Cell Behavior

Stem cells occupy a central position in regenerative medicine because of their capacity for self-renewal, multilineage differentiation, and participation in tissue repair. Their biological behavior is highly dependent on signals originating from the surrounding microenvironment, including biochemical factors, extracellular matrix composition, mechanical properties, topographical features, and cell–cell interactions. Nanoengineered materials provide a unique opportunity to regulate these signals because their dimensions and surface characteristics can be tailored to the nanoscale features of the native cellular microenvironment. Consequently, interactions between nanomaterials and stem cells represent an important extension of the nano–bio interface and provide a mechanistic link between material design and tissue regeneration.

Unlike conventional culture substrates, nanostructured materials can simultaneously provide physical, chemical, and mechanical cues to stem cells. These cues may regulate cell adhesion, cytoskeletal organization, proliferation, migration, metabolism, and lineage commitment. Importantly, the effects of nanomaterials on stem cells are not determined by a single material property. Instead, stem-cell responses emerge from the combined influence of surface chemistry, nanoscale topography, stiffness, surface energy, protein adsorption, cellular receptors, and intracellular signaling. Understanding these interconnected mechanisms is therefore essential for developing nanoengineered microenvironments capable of guiding stem-cell behavior in a predictable manner. As illustrated in *Fig. 3*, nano–bio interfaces guide stem-cell fate through a sequential cascade of integrin engagement, cytoskeletal remodeling, and transcriptional regulation [36].

6.1 | Stem-Cell–Nanomaterial Interactions

The initial interaction between stem cells and nanomaterials occurs at the cell–material interface and is mediated by a combination of adhesion molecules, membrane receptors, extracellular matrix proteins, and physicochemical interactions. Integrins represent particularly important mediators because they connect extracellular adhesion molecules with the intracellular cytoskeleton and participate in the transmission of mechanical and biochemical signals.

When stem cells encounter a nanostructured surface, adsorption of proteins and extracellular matrix components can create molecular bridges between the material and cellular receptors. The organization and density of these molecules can influence focal adhesion formation, cell spreading, cytoskeletal organization, and downstream signaling. Because the nanoscale arrangement of adhesion sites can differ substantially between engineered materials, nanostructured surfaces may provide cellular cues that cannot be reproduced by conventional planar substrates.

The biological response is also influenced by the composition and organization of the nano–bio interface. Protein corona formation, surface hydration, charge, and nanoscale curvature can modify receptor accessibility and the strength of cell–material interactions. Thus, the response of stem cells to a nanomaterial should be interpreted within the broader framework of the biological interface established after exposure rather than solely on the basis of the pristine material surface [37].

6.2 | Nanomaterial-Mediated Regulation of Stem-Cell Proliferation

Stem-cell proliferation is regulated by a complex network of growth signals, cell-cycle regulators, metabolic pathways, and environmental cues. Nanomaterials can influence these processes by modifying cell adhesion, intracellular signaling, mechanical stimulation, and local biochemical interactions. Nanoscale surface features can alter the organization of focal adhesions and cytoskeletal tension, which in turn may influence signaling pathways associated with cell-cycle progression. Surface chemistry can additionally affect the adsorption and presentation of proteins that participate in cell growth and adhesion. These effects may create microenvironments that either support stem-cell expansion or promote progression toward differentiation.
The relationship between nanomaterial characteristics and proliferation is not necessarily linear. Highly interactive surfaces may promote strong adhesion, but excessive interaction can also increase cellular stress. Similarly, changes in surface stiffness or topography may promote proliferation within a particular range but become unfavorable beyond a certain threshold. Consequently, rational material design requires identification of the range of physicochemical properties that support stem-cell viability and functional activity. An additional consideration is the balance between proliferation and differentiation. In regenerative medicine, maximizing cell number is not always the primary objective. Depending on the therapeutic strategy, preservation of stemness or controlled progression toward a specific lineage may be more important than unrestricted proliferation. Nanomaterials should therefore be designed according to the desired biological endpoint rather than proliferation alone [28], [36], [37].

6.3 | Nanotopography and Stem-Cell Adhesion

The nanoscale architecture of the extracellular environment provides important physical cues to stem cells. Native extracellular matrices contain fibers, pores, ridges, grooves, and molecular structures that exist across multiple length scales. Nanostructured biomaterials can reproduce selected aspects of this organization and thereby influence cell adhesion and morphology.

Nanotopography can affect the number, size, distribution, and maturation of focal adhesions. These changes influence cytoskeletal organization and cellular contractility and can subsequently alter intracellular signaling. Depending on feature size, geometry, spacing, and orientation, nanostructured surfaces may promote cell spreading, elongation, alignment, or changes in cellular polarity. These morphological changes can be biologically significant because stem-cell shape and cytoskeletal tension are closely associated with lineage

specification. A surface that promotes an elongated cellular morphology may generate signaling patterns distinct from those induced by a surface supporting a rounded morphology. Thus, nanoscale topography can function as an indirect regulator of stem-cell fate by modifying the physical state of the cell. Importantly, topographical cues interact with biochemical and mechanical signals. The same nanostructure may produce different biological responses depending on the underlying substrate stiffness, surface chemistry, and extracellular protein composition. A comprehensive understanding of stem-cell responses therefore requires consideration of nanotopography as part of an integrated microenvironment rather than as an isolated design parameter [21].

6.4 | Mechanotransduction and Stem-Cell Fate

Mechanotransduction represents one of the most important mechanisms through which nanomaterials can influence stem-cell fate. Stem cells continuously sense mechanical properties of their environment through integrins, focal adhesions, the actin cytoskeleton, mechanosensitive ion channels, and associated signaling proteins. These mechanical signals are subsequently converted into biochemical responses that regulate gene expression and cell fate. At the cell–material interface, integrin clustering can activate focal adhesion-associated signaling pathways, including Focal Adhesion Kinase (FAK) and Src-family kinases. These pathways interact with the cytoskeleton and regulate actomyosin contractility. Changes in cytoskeletal tension can subsequently influence transcriptional regulators, including the Yes-associated protein (YAP)/TAZ pathway, which plays an important role in mechanosensitive control of cell behavior.

Nanomaterial properties can regulate stem-cell fate through a cascade involving integrin engagement, focal adhesion formation, cytoskeletal remodeling, intracellular mechanotransduction, and transcriptional regulation, thereby influencing differentiation even in the absence of conventional biochemical cues. The mechanical environment is particularly important because different tissues possess distinct mechanical characteristics. Materials designed for bone regeneration may require substantially different mechanical cues from those intended for neural or cardiac tissue engineering. Consequently, tissue-specific nanomaterial design should consider the mechanical environment of the target tissue and how it interacts with nanoscale surface features [22].

6.5 | Nanomaterials and Lineage-Specific Differentiation

One of the most extensively investigated applications of nanomaterials in regenerative medicine is the regulation of stem-cell differentiation. By providing appropriate combinations of topographical, mechanical, electrical, and biochemical cues, nanostructured materials can influence the commitment of stem cells toward specific tissue lineages [21].

6.5.1 | Osteogenic differentiation

Nanostructured materials have received considerable attention for bone regeneration because the native bone extracellular matrix contains nanoscale mineralized structures. Nanomaterials can reproduce aspects of this hierarchical organization and provide physical and biochemical cues that favor osteogenic differentiation. Surface roughness, nanoscale mineral features, mechanical stiffness, and the presentation of calcium- and phosphate-associated signals can influence osteogenic pathways. Changes in integrin signaling and cytoskeletal organization may further activate transcriptional programs associated with osteoblast differentiation. The similarity between nanoscale engineered structures and the architecture of native bone extracellular matrix provides a strong biological rationale for the use of nanostructured interfaces in osteogenic tissue engineering [19].

6.5.2 | Chondrogenic differentiation

Cartilage presents a distinct regenerative challenge because of its specialized extracellular matrix and limited intrinsic healing capacity. Nanostructured biomaterials can provide extracellular cues that influence stem-cell condensation, adhesion, and chondrogenic commitment. The interaction between nanoscale topography and

matrix-associated signaling may regulate cytoskeletal organization and cell–cell interactions, both of which are important during chondrogenesis. However, excessive mechanical stimulation or inappropriate surface characteristics may promote alternative differentiation pathways. Therefore, the design of nanostructured cartilage-regeneration platforms requires careful control of mechanical and topographical signals [28].

6.5.3 | Neurogenic differentiation

Neural tissues possess distinctive mechanical and topographical environments that differ substantially from those of mineralized tissues. Nanostructured surfaces can provide directional and topographical cues that influence neuronal adhesion, cytoskeletal organization, neurite extension, and neural differentiation. Aligned nanofibers, nanoscale grooves, and other anisotropic structures can provide spatial guidance for developing neuronal processes. Such architectures may be particularly valuable for promoting organized cellular alignment and connectivity within engineered neural tissues. The mechanical softness of neural tissue also highlights the importance of integrating nanoscale topography with appropriate bulk mechanical properties. A highly structured nanosurface alone may be insufficient if the underlying material exhibits mechanical characteristics that are incompatible with the target neural environment [38].

6.5.4 | Cardiogenic differentiation

Cardiac regeneration requires coordination between cell differentiation, electrical signaling, mechanical stimulation, and tissue organization. Nanostructured materials can contribute to this process by providing electrical or mechanical cues and by promoting alignment of cells within engineered microenvironments.

Surface architecture can influence cardiomyocyte morphology and organization, while conductive nanomaterials may facilitate electrical communication between cells. At the same time, mechanical properties can influence contractile behavior and maturation. These combined effects illustrate the importance of designing multifunctional nano–bio interfaces that reproduce multiple aspects of the native cardiac environment [26].

6.5.5 | Adipogenic differentiation

Although adipogenic differentiation is not always a primary target in regenerative engineering, it provides an important example of the context-dependent nature of nanomaterial effects. Changes in substrate stiffness, surface chemistry, and cell morphology can influence the balance between adipogenic and alternative differentiation pathways.

The ability of nanostructured interfaces to alter cell shape and mechanical signaling therefore provides opportunities for regulating adipogenic commitment. This finding further supports the broader concept that nanoscale material cues can influence stem-cell fate by modifying the physical and molecular microenvironment [39].

6.6 | Nanomaterials and Stem-Cell Migration

Stem-cell migration is essential for effective tissue repair because cells must reach sites where regeneration is required. Nanomaterials can influence migration through changes in surface adhesion, cytoskeletal organization, topographical guidance, and chemotactic signaling.

Nanofibrous and anisotropic structures can provide directional cues that guide cell movement. Such contact-guidance effects are particularly relevant for tissues with highly organized architectures, including neural, muscle, and vascular tissues. The relationship between adhesion and migration is complex. Strong cell adhesion may improve cell retention but can also reduce migration if cells become excessively anchored to the material surface. Conversely, insufficient adhesion may impair cell survival and directional movement. The optimal interface must therefore balance adhesion strength with dynamic cytoskeletal remodeling. Nanomaterials may also influence migration indirectly through interactions with immune cells and extracellular matrix components. Cytokines released by immune cells can alter stem-cell recruitment, while

changes in matrix organization can create new migratory pathways [31]. Thus, stem-cell migration should be considered within the broader cellular and immunological microenvironment.

6.7 | Nanomaterials and Stem-Cell Metabolism

Cellular metabolism is increasingly recognized as an important regulator of stem-cell fate. Stem cells can undergo metabolic transitions during differentiation, with changes in glycolysis, mitochondrial activity, oxidative phosphorylation, and redox balance accompanying shifts in cellular identity.

Nanomaterials may influence stem-cell metabolism through interactions with mitochondria, intracellular signaling pathways, cellular adhesion, and mechanical cues. Changes in substrate properties can alter energy requirements associated with cytoskeletal remodeling, while intracellular nanomaterial accumulation may influence mitochondrial function and oxidative signaling.

Controlled modulation of metabolism may contribute to regenerative responses, whereas excessive metabolic stress can compromise stem-cell function. Therefore, metabolic compatibility should be considered alongside conventional measures of viability and differentiation when evaluating nanoengineered stem-cell interfaces [40].

An emerging perspective is that nanomaterials may regulate stem-cell fate not only through classical growth-factor-associated pathways but also through the integration of mechanical, metabolic, and redox signals. This broader view may provide new opportunities for designing materials capable of influencing cell fate without relying exclusively on exogenous biochemical stimulation.

6.8 | Immune–Nanomaterial–Stem Cell Crosstalk

Stem-cell behavior within regenerative tissues is strongly influenced by the immune microenvironment, meaning that the effects of nanomaterials cannot always be understood solely through direct cell–material interactions. Nanomaterials may first interact with immune cells, particularly macrophages, and subsequently modify the cytokine, chemokine, and extracellular matrix environment surrounding stem cells, thereby influencing their proliferation, migration, and differentiation. A nanomaterial that promotes an appropriate reparative immune response may create a microenvironment favorable for stem-cell-mediated regeneration, whereas persistent inflammatory activation may impair stem-cell survival and differentiation. This interaction is multidirectional, as stem cells can also modulate immune responses through the secretion of immunomodulatory molecules and extracellular vesicles, creating feedback mechanisms that influence the overall regenerative outcome. Therefore, understanding the nanomaterial–immune cell–stem cell axis is essential for designing next-generation biomaterials capable of regulating the broader cellular microenvironment rather than targeting stem cells and immune cells independently [39].

6.9 | Challenges in Controlling Stem-Cell Fate Using Nanomaterials

Despite significant progress, precisely predicting and controlling stem-cell responses to nanomaterials remains challenging because multiple material properties can simultaneously influence cellular behavior. In addition, differences in stem-cell source, donor, passage number, metabolic state, and culture conditions can lead to variable responses. Many studies also rely on simplified two-dimensional models that do not adequately reproduce the three-dimensional architecture, mechanical cues, immune interactions, and biochemical gradients of regenerating tissues. Therefore, advanced models such as three-dimensional cultures, organoids, organ-on-chip platforms, and multicellular systems may provide more physiologically relevant insights. Standardized characterization of nanomaterial size, morphology, surface chemistry, charge, aggregation, and exposure conditions is also essential for establishing reproducible structure–function relationships. Future research should move toward predictive nano–bio engineering through the integration of high-throughput screening, single-cell analysis, advanced imaging, computational modeling, and machine learning. Effective control of stem-cell fate requires coordinated regulation of physical, chemical, mechanical, and biological

signals while considering the surrounding immune microenvironment. These principles provide the basis for applying nano–bio interfaces to tissue-specific regeneration [40].

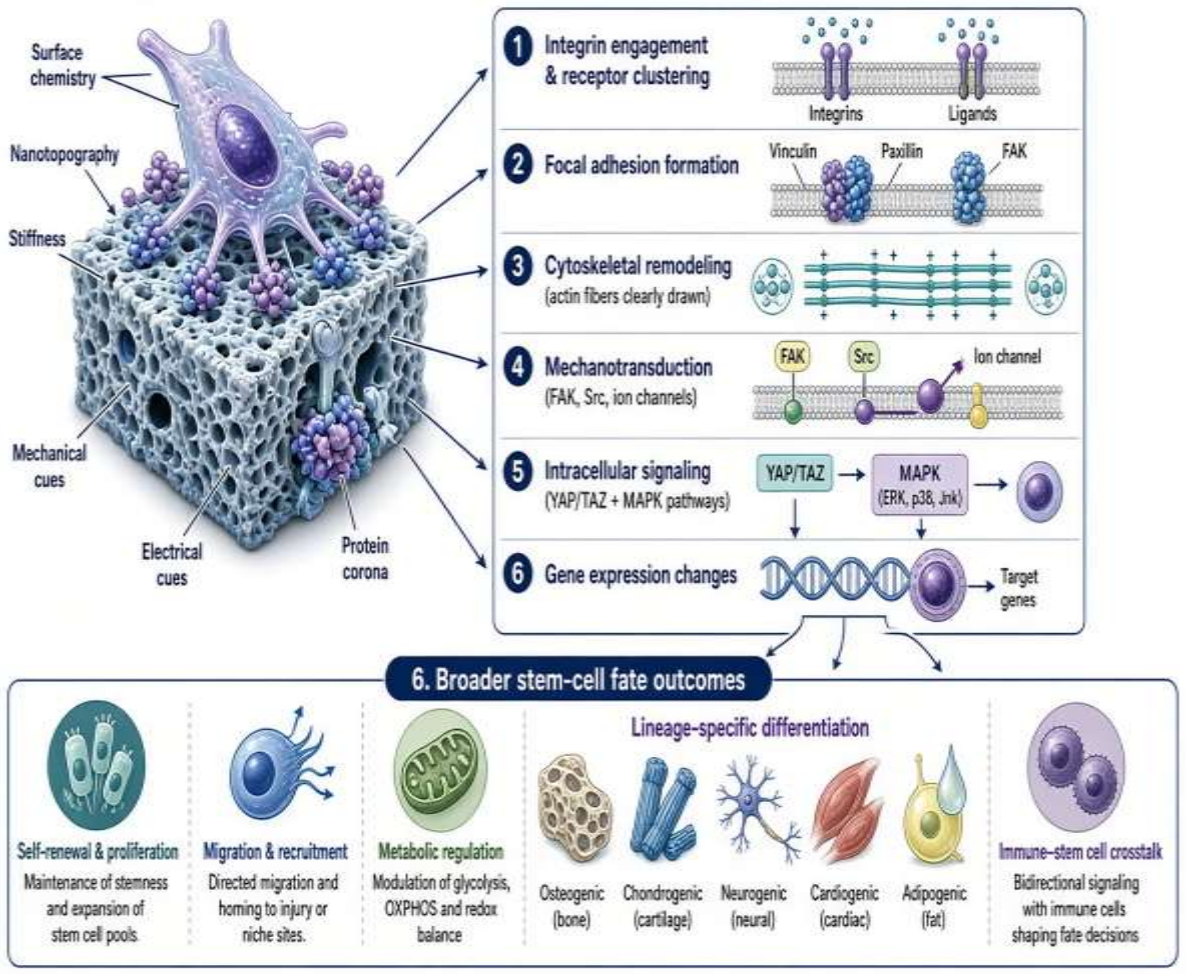

Fig. 3. Mechanistic cascade showing how nanomaterial properties regulate stem-cell fate through integrin-mediated mechanotransduction and downstream signaling.

7 | Nano–Bio Interfaces in Tissue-Specific Regeneration

The biological effects of nano–bio interactions become particularly important when nanomaterials are incorporated into tissue-engineering systems. Because different tissues possess distinct extracellular matrix architectures, mechanical properties, cellular compositions, and immune environments, nanomaterial design must be adapted to the specific requirements of each tissue .As illustrated in *Fig. 4* and *Table 4*, these tissue-specific differences require nano–bio interfaces to be tailored according to the structural, mechanical, cellular, and immunological characteristics of the target tissue.

Nanoengineered interfaces can support regeneration by regulating cell adhesion, mechanotransduction, stem-cell differentiation, extracellular matrix organization, immune responses, and vascularization [28].

7.1 | Bone Regeneration

Bone provides a natural nanoscale environment consisting of mineral structures closely associated with collagen. Nanostructured materials can mimic selected aspects of this architecture through nanoscale mineralization, surface patterning, and fibrous structures, thereby influencing cell adhesion, mechanotransduction, and osteogenic differentiation. Regulation of macrophage behavior and vascularization is also important for successful bone formation. Future systems should therefore integrate osteogenic,

immunomodulatory, and angiogenic signals while maintaining appropriate mechanical strength and biodegradability [35].

7.2 | Cartilage Regeneration

Cartilage possesses a specialized extracellular matrix and a distinctive mechanical environment, while its limited vascularization contributes to its poor regenerative capacity. Nanofibrous and nanoscale architectures can provide structural and biochemical cues that support chondrogenic differentiation and extracellular matrix formation. Because inappropriate mechanical properties or excessive inflammatory signaling may impair regeneration, effective materials should combine suitable nanoscale organization, mechanical behavior, and immune regulation [41].

7.3 | Neural Regeneration

Neural regeneration requires precise control of mechanical, topographical, biochemical, and electrical signals. Aligned nanofibers and nanoscale patterns can provide directional guidance for neuronal organization and neurite extension, while appropriate mechanical properties are essential because neural tissues are relatively soft. Conductive nanomaterials may additionally provide electrical cues, although their properties must be carefully controlled to maintain biocompatibility. Interactions with glial and immune cells should also be considered when designing neural nano–bio interfaces [40].

7.4 | Cardiac Regeneration

Cardiac regeneration requires coordinated restoration of cellular organization, electrical conduction, mechanical function, and vascularization. Nanostructured materials can promote cardiogenic differentiation and directional cellular organization, while conductive nanomaterials may facilitate electrical communication between cardiac cells. Appropriate mechanical properties and vascular support are equally important. Thus, multifunctional interfaces capable of coordinating electrical, mechanical, vascular, and immunological signals may provide greater regenerative potential than materials targeting cardiomyocyte differentiation alone [41].

7.5 | Vascular Regeneration

Vascular regeneration depends on coordinated interactions among endothelial cells, smooth muscle cells, extracellular matrix, and immune populations. Nanoscale surface features can regulate endothelial adhesion, migration, alignment, and organization, while appropriate surface chemistry and mechanical properties help reproduce the vascular microenvironment. Because immune and stromal cells also regulate angiogenesis, nanoengineered materials should consider both direct endothelial responses and indirect immunological effects [42].

7.6 | Skin and Soft-Tissue Regeneration

Skin regeneration requires coordinated activity of keratinocytes, fibroblasts, endothelial cells, immune cells, and extracellular matrix components. Nanofibrous structures can support cellular organization and matrix deposition, while regulation of inflammatory responses may facilitate the transition from inflammation to tissue remodeling. Angiogenesis is also essential for effective repair. An important challenge is therefore to balance matrix formation and remodeling to promote regeneration while minimizing excessive fibrosis and scar formation [35].

7.7 | Cross-Tissue Principles of Nano–Bio Interface Design

Despite differences among tissues, several common principles can be identified. Nanomaterial properties should be matched to the mechanical and biological characteristics of the target tissue, while cellular and immune responses should be considered together. Nanoscale cues should also be integrated with larger-scale architecture to reproduce the hierarchical organization of native tissues. Furthermore, because regeneration

is a dynamic process, materials capable of adapting their degradation, surface properties, or mechanical behavior over time may offer advantages over static systems [36].

7.8 | Comparative Perspective

The tissue-specific applications demonstrate that nanomaterial effects are strongly context-dependent. Bone requires mineralization and mechanical support, neural tissues require soft and directional cues with potential electrical functionality, cardiac tissues require coordinated electrical and mechanical signaling, vascular tissues depend on endothelial organization and biomechanical compatibility, and skin requires barrier restoration, angiogenesis, and controlled inflammation. Therefore, rather than pursuing a universal nanomaterial, future research should focus on tissue-specific nano–bio interface engineering, in which material properties are selected according to the biological requirements of each regenerative environment.

Nano–bio interfaces provide a versatile connection between material design and tissue-specific cellular and immunological processes. Their ability to regulate cellular behavior, extracellular matrix organization, immune responses, and tissue architecture creates opportunities for more integrated regenerative strategies [37]. However, successful translation requires understanding not only how nanomaterials promote regeneration but also their degradation, persistence, biodistribution, and long-term biological fate, which is addressed in the following section.

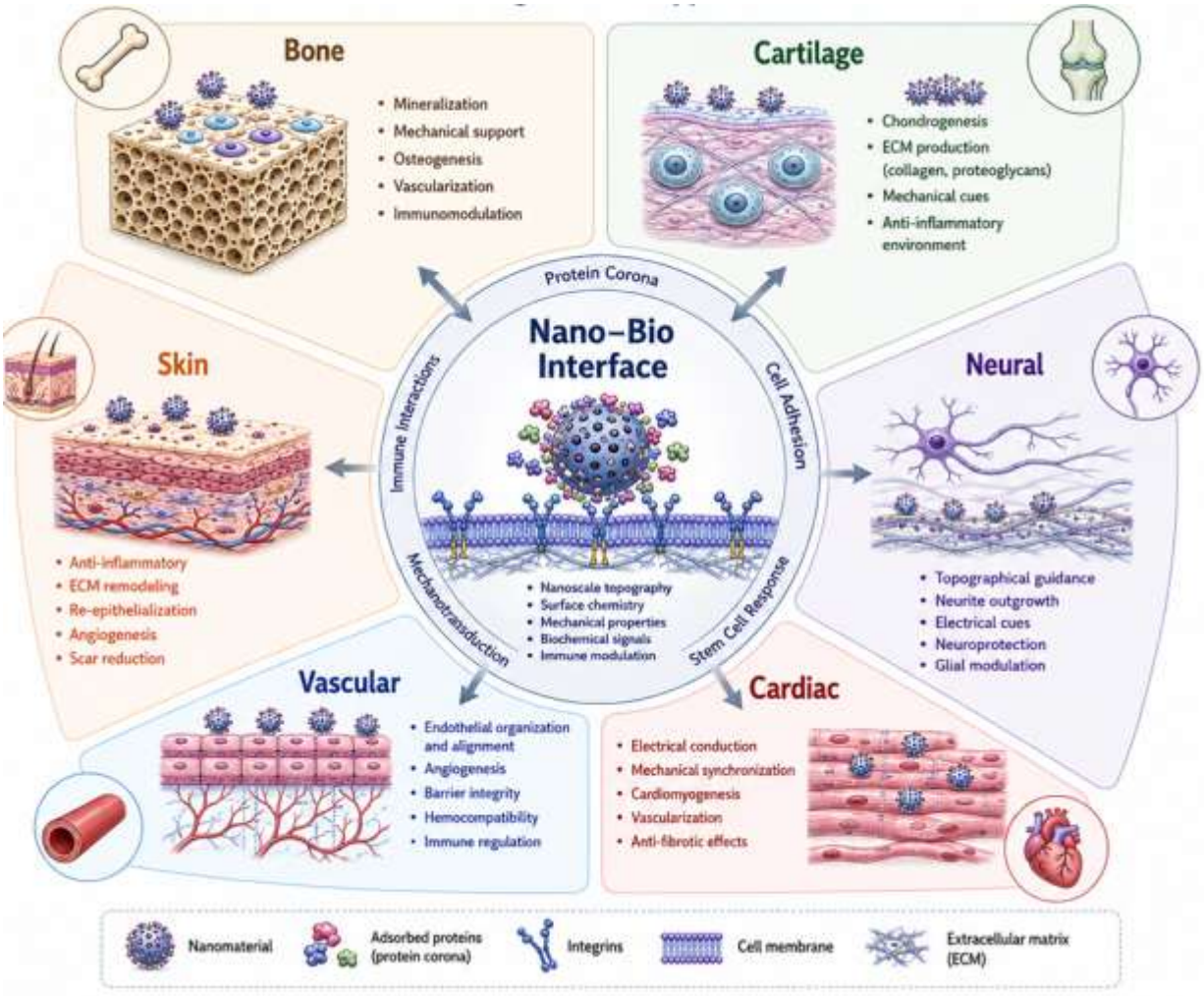

Fig. 4. Tissue-specific design principles of nano–bio interfaces for regenerative applications.

Table 4. Tissue-specific design principles of nano–bio interfaces.

Tissue	Key Biological Requirements	Important Nano–Bio Cues	Major Regenerative Targets
Bone	Mineralized ECM, mechanical strength, vascularization	Nanostructured mineralization, topography, stiffness	Osteogenesis, angiogenesis, immune modulation
Cartilage	Specialized ECM, low vascularity, mechanical loading	Nanofibrous architecture, mechanical cues, biochemical signals	Chondrogenesis, ECM formation
Neural tissue	Soft mechanics, directional organization, electrical signaling	Aligned nanostructures, topographical and electrical cues	Neurite extension, neuronal differentiation
Cardiac tissue	Electrical conduction, mechanical activity, vascularization	Conductive nanostructures, aligned architecture, mechanical cues	Cardiomyogenesis, electrical coupling, vascularization
Vascular tissue	Endothelial organization, blood compatibility, mechanical stability	Surface chemistry, nanoscale topography, mechanical cues	Endothelial adhesion, alignment, angiogenesis
Skin	Barrier restoration, ECM remodeling, vascularization, controlled inflammation	Nanofibrous structures, surface cues, immunomodulation	Re-epithelialization, ECM remodeling, wound healing

8 | Biological Fate, Safety, and Translational Challenges of Nanomaterials

The biological performance of nanomaterials is determined not only by their ability to regulate cellular behavior and tissue regeneration but also by their fate within biological environments. Following exposure, nanomaterials may undergo degradation, cellular uptake, redistribution, persistence, or clearance. These processes can substantially influence both their regenerative efficacy and long-term safety [34].

8.1 | Degradation, Persistence, and Clearance

The degradation behavior of nanomaterials is a critical determinant of their biological fate. Depending on their composition, nanomaterials may undergo hydrolysis, oxidation, enzymatic degradation, dissolution, or structural fragmentation. For biodegradable systems, degradation can provide temporary biological and structural functions while reducing long-term material accumulation. However, excessively rapid degradation may compromise regenerative activity, whereas prolonged persistence may increase the risk of chronic cellular or immune responses. Importantly, degradation products should also be considered because soluble molecules, ions, or nanoscale fragments may exhibit biological effects distinct from those of the original material. Therefore, evaluation of nanomaterial safety should include both the parent material and its degradation products [35].

8.2 | Long-Term Biocompatibility and Nanotoxicity

Although many nanomaterials demonstrate acceptable short-term cytocompatibility, long-term biological effects remain an important concern. Persistent exposure or intracellular accumulation may influence oxidative balance, mitochondrial function, inflammatory signaling, genomic stability, and tissue homeostasis. ROS represent one of the most frequently investigated mechanisms of nanomaterial-associated cellular stress. Moderate redox signaling may participate in physiological cellular regulation, whereas excessive or prolonged oxidative stress can impair cell function and compromise tissue regeneration. The biological response is strongly dependent on particle size, morphology, surface chemistry, concentration, and exposure duration. Consequently, nanotoxicity should not be considered an intrinsic property of a material alone but rather as the result of a dynamic interaction between material characteristics and the biological environment [36].

8.3 | Translational Challenges

Despite considerable progress in experimental studies, translation of nanoengineered materials from laboratory research to clinical applications remains challenging. Conventional two-dimensional cell cultures cannot fully reproduce the complex interactions among immune cells, extracellular matrix, blood vessels, mechanical forces, and tissue-specific microenvironments.

Animal models provide greater biological complexity but may not completely reproduce human immune responses, metabolism, or tissue architecture. Differences in nanomaterial synthesis, particle size distribution, surface chemistry, aggregation, and degradation can further contribute to variability between studies. Manufacturing and sterilization also represent important translational considerations. Processes used for large-scale production or sterilization may alter the physicochemical characteristics of nanomaterials and consequently modify their biological behavior. Standardized characterization and reproducible manufacturing protocols are therefore essential for successful translation [27].

8.4 | Future Perspectives

Future research should move beyond the concept of passive biocompatibility toward the development of predictive and biologically instructive nano–bio interfaces. Advanced three-dimensional models, organ-on-chip systems, single-cell analysis, spatial omics, and computational approaches may provide more accurate predictions of nanomaterial behavior in complex biological environments. Integration of artificial intelligence with standardized nanomaterial datasets may further facilitate the identification of relationships between physicochemical properties and biological outcomes. In parallel, dynamic and stimuli-responsive nanomaterials could provide spatially and temporally controlled signals that adapt to different stages of tissue regeneration. Ultimately, successful regenerative nanomaterials should provide an appropriate balance between biological activity, degradation, immune compatibility, and long-term safety. The future direction of the field is therefore likely to shift from designing materials that are merely biocompatible toward materials that are biologically instructive, adaptive, and predictable [42]. The major challenges and emerging strategies for advancing nano–bio interface engineering toward predictable and clinically translatable regenerative applications are summarized in *Table 5*.

Table 5. Major challenges and emerging strategies in nano–bio interface engineering.

Challenge	Current Limitation	Emerging Strategy	Expected Outcome
Dynamic protein corona	Difficult prediction of biological identity	Corona engineering and advanced profiling	More predictable cellular responses
Cell-type variability	Different cells respond differently to identical materials	Multicellular and patient-relevant models	Improved biological predictability
Simplified 2D models	Poor representation of tissue microenvironment	3D models, organoids, organ-on-chip	More physiologically relevant evaluation
Complex immune responses	Difficult control of inflammation	Immunomodulatory nano–bio interfaces	Improved tissue regeneration
Uncontrolled intracellular accumulation	Potential cellular stress	Controlled uptake and degradation	Improved safety
Tissue-specific requirements	No universal material design	Tissue-specific nanoengineering	Better regenerative performance
Limited structure–function predictability	Multiple material properties interact simultaneously	AI, machine learning, and high-throughput screening	Predictive material design
Translation to clinical applications	Differences between laboratory and biological environments	Standardized characterization and advanced models	Improved reproducibility and translation

9 | Conclusion

Nanomaterials have emerged as powerful platforms for regulating biological processes at multiple length scales, from molecular interactions and cellular signaling to tissue organization and regeneration. Their unique physicochemical properties enable the creation of interfaces capable of interacting with proteins, cell membranes, immune cells, stem cells, and extracellular matrix components [23–25]. However, the biological behavior of nanomaterials cannot be understood solely from their intrinsic physicochemical characteristics. Once introduced into a biological environment, their surface is dynamically transformed through protein adsorption, cellular interactions, degradation, and immune recognition, creating a continuously evolving nano–bio interface. This review highlights the importance of considering nano–bio interactions as a dynamic and interconnected process. The formation of the protein corona can modify the biological identity of nanomaterials, while subsequent interactions with cell membranes and intracellular compartments determine their uptake and cellular fate [26]. At the same time, interactions with the immune system can influence

inflammation, macrophage behavior, tissue remodeling, and ultimately regenerative outcomes. These processes are closely connected with stem-cell responses, including adhesion, proliferation, migration, mechanotransduction, metabolism, and lineage-specific differentiation. An important emerging concept is that successful regenerative nanomaterials should not simply avoid biological interactions. Instead, they should be designed to regulate and instruct biological responses actively. Through appropriate control of surface chemistry, nanotopography, mechanical properties, degradation behavior, and spatial organization, nanomaterials can provide signals that guide cellular and immune behavior toward tissue-specific regeneration [36]. The tissue-specific applications discussed in this review further demonstrate that there is no universal nano–bio interface suitable for all regenerative applications. Bone, cartilage, neural, cardiac, vascular, and skin tissues possess distinct mechanical, biochemical, structural, and immunological environments. Therefore, future nanomaterial design should increasingly adopt a tissue-specific and mechanism-driven strategy in which material properties are selected according to the biological signals required for functional regeneration. Despite significant progress, important challenges remain before these approaches can be widely translated into clinical practice. Variations in nanomaterial synthesis, characterization, biological models, experimental conditions, and degradation behavior continue to limit reproducibility and comparison between studies. Furthermore, long-term biodistribution, persistence, immune responses, degradation products, and potential nanotoxicity require more comprehensive investigation. Advanced three-dimensional models, organ-on-chip systems, single-cell and spatial omics, high-resolution imaging, and computational approaches may help overcome some of these limitations [31–37].

Looking forward, the field is expected to move toward predictive, adaptive, and personalized nano–bio engineering. Integration of nanotechnology with artificial intelligence, multi-omics, advanced biomaterials, and patient-specific biological models could enable the rational design of interfaces with predefined cellular and tissue responses. Dynamic and stimuli-responsive nanomaterials may further allow biological signals to change according to the evolving requirements of tissue repair. Ultimately, the next generation of regenerative nanomaterials should be viewed not merely as structural scaffolds or passive carriers, but as dynamic biological interfaces capable of communicating with cells and tissues. The successful convergence of nanotechnology, materials science, cell biology, immunology, and regenerative medicine may therefore provide a pathway toward safer, more predictable, and functionally integrated tissue regeneration.

Authors' Contributions

The author solely conducted the research and prepared the manuscript and has approved its final version.

Data Availability

The data are available from the corresponding author upon reasonable request.

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Conflict of Interest

There are no competing interests to declare.

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This article does not include experiments involving humans or animals.

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