

Original Article



Engineering nanotherapeutics to target mechanotransduction, senescence, and regenerative signaling

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Abstract

The complex nature of wound healing is influenced by a variety of factors such as mechanotransduction, inflammation, cellular senescence, remodeling of the extracellular matrix, and signaling in regenerative mechanisms. Disruption in mechanotransduction can alter the cellular activities, gene expression, and tissue architecture and can lead to chronic non-healing wounds due to a range of issues. Nanotechnology has made it possible to resolve these issues through a better understanding of the processes involved. By using different types of nanocarriers such as liposomes, polymeric nanoparticles, and multifunctional nanostructures, it is possible to deliver drugs efficiently and in a way that would prevent them from destruction in the wound environment. The functional nanoparticles and nanozymes are able to produce their antimicrobial, antibiofilm, and antioxidant effect which creates comfortable conditions for the processes taking place in tissues. New innovations in nanomedicine take into account issues of the cellular aging and inflammatory processes while ensuring that they do not influence healthy cells. Multifunctional platforms also contribute to the modulation of signaling of growth factors, transcriptional activity, and calcium-dependent pathways involved in rejuvenation. Immunomodulatory nanotherapies may support the polarization of macrophages to pro-reparative phenotypes and regulate the activity of neutrophils, while smart systems with the ability to sense pathological biomarkers may enable adaptive treatment of wounds. In total, these methods contribute to the comprehensive regulation of the mechanical, inflammatory, and regenerative aspects of wound healing. Nevertheless, strict preclinical and clinical evaluation of different types of wounds is necessary before establishing their safety, effectiveness, and possibility of practical application.

Keywords

Cell mechanotransduction, nanotherapeutics, liposomes, nanoparticles, regenerative therapies, intracellular signaling pathways, wound healing, tissue regeneration.

Introduction

The wound healing models offer unique opportunities to explore the molecular and cellular features underlying wound repair. Treatment of wounds and their management is inefficient although numerous available medications are present. Conventional therapeutics have insufficient efficacy in treatment of different wounds such as the traditional ones including gene therapy, cell therapy and other treatments.^[1] Thus, the need for innovative treatment approaches has become inevitable and the emergence of technological therapeutics

such as nanotherapeutics, bioengineered skin substitutes, 3D bioprinting of skin substitutes and stem cell therapy.^[2] Skin wound healing can be accelerated by increasing the activity of signaling molecules like calcium and gasotransmitters. Gasotransmitters, in this case, are bioactive agents, which penetrate cells and have presented themselves with antioxidative effects that are known for boosting up the healing processes. Calcium supplements, in their turn, have positive effect on immune function boosting up the healing pace. Chronic wounds related to diabetes mellitus and certain in-

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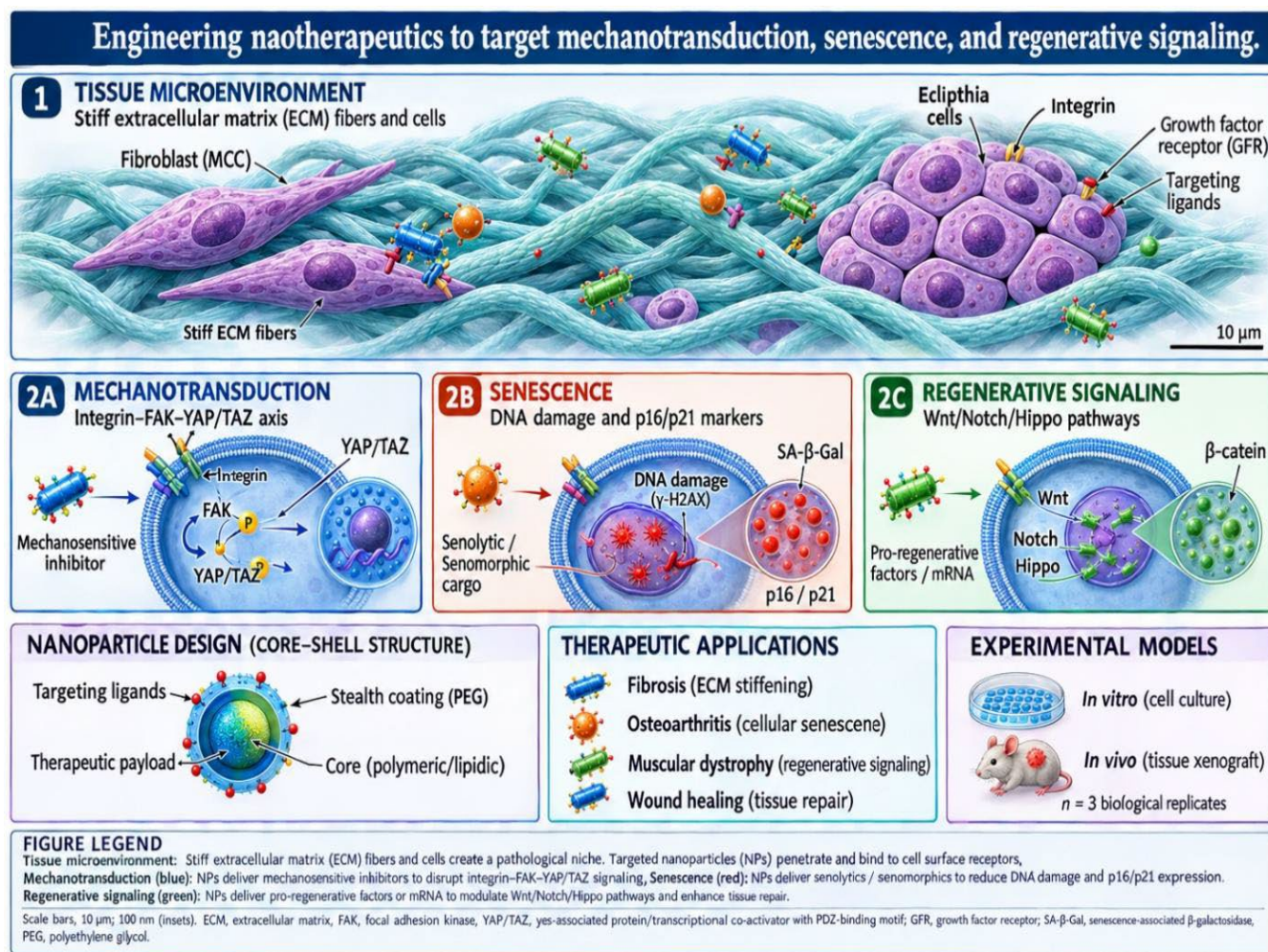


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flammatory illnesses require treatment of special nature. It is important to mention that Wnt and notch signaling pathways are responsible for the determination of cell destiny in the process of skin regeneration, in particular wound healing. To establish this proof-of-concept, strategies grounded in genetics, treatment response, and phenotypic characterization must be employed as both preventative and regenerative therapeutic approaches. This underscores the need for continued research and preventive measures in this field, as well as a deeper understanding of the molecular mechanisms underlying healing responses and impairments observed in animal models. Ultimately, translating these therapies into clinical practice will require well-defined clinical objectives, efficient and well-designed human trials, accurate patient diagnosis, and a thorough understanding of individual heterogeneity.^[3] Recent innovations in nanotechnology have provided

valuable insights into the functions and processes of cells. With these new tools and technologies, scientists have effectively created a new kind of regenerative medicine. These nanotherapeutics serve to enhance the way cells communicate mechanically so that damaged organs and tissues can be revived with the help of advanced nanodevices and tools.^[4] Nanoparticles have the ability to modify mechanotransduction machines because of the specific physical and chemical features they provide for the preparation of preventative and regenerative medicine.^[5] The advancement of these technologies in medicine enables the development of new therapies that facilitate the successful delivery of nanomedicines where they are needed. For creating new practices in the field of medicine, contemporary nanoparticles and their derivatives have been used in order to develop new biomaterials for wound healing and tissue repair.

Graphical abstract



Engineering nanotherapeutics to target mechanotransduction, cellular senescence, and regenerative signaling.

Aging of cells occurs when cells attain their maximum ability to divide and stop doing so, without going through destruction. This condition almost invariably plays a very important role in different biological processes, such as tissue repair, aging, and more.^[6] As per findings, prolonged and persistent cellular senescence is observed in the case of chronic wounds, while initial stages of wound healing is characterized by stimulated functional activity and differentiation of fibroblasts. The complexity of physiological role of cellular senescence is illustrated in the process of cutaneous wound healing, as senescent phenotypes show contradictory effects due to the timing of appearance, content, and nature of cells in order for wound closure to take place successfully. The nanotherapeutics take advantage of bio/nanomaterials that stimulate natural healing processes taking into account genetic, phenotypic, and cellular aspects.^[7] These bio-inspired hybrid/composite nanomaterials will benefit the expansion of (i) preventive and regenerative medicine for tissue, organ, and bone regeneration; (ii) bioimaging agents with enhanced mechanical stability; (iii) biocompatibility and antimicrobial effectiveness; (iv) delivery of drugs, growth factors, and genetic material to promote tissue regeneration; and (v) cell imaging and stem cell tracking with built-in regenerative capabilities.^[8] Nanotherapeutic platforms (such as liposomes and polymeric nanoparticles), exhibit a number of advantages in terms of their physical and chemical properties and their ability to cross various biological barriers.

Biomechanical signals generated by nanotherapeutics contribute to restoring normal cellular activities. At the same time, targeted mechanisms of action of these materials can reverse the process of cellular senescence whilst regulating crucial signaling pathways via controlled release of therapeutic agents. These characteristics make nanotherapeutics effective therapeutic agents for improving tissue repair and regeneration, but the underlying mechanisms still require further studies. This review highlights the intracellular signal transduction pathways together with cell mechanotransduction which include wound healing; the physical, chemical and biochemical processes contributing to the cell mechanotransduction; the diseases associated with flawed signaling and the possibility of recovering cell functions; the role of calcium signals and cellular aging in wound repair as potentially critical regulators of the healing process; and the novel functions performed by neutrophilic cells in the healing process and tissue repair.^[9] Moreover, the review briefly describes the advanced nanomedicine techniques aimed at improving the wound healing and the tissue recovery through influencing and reprogramming critical cellular processes (e.g., mechanotransduction and cellular senescence).

Cellular Mechanotransduction and Intracellular Signaling Pathways in Wound Healing: Current Insights and Emerging Perspectives

A reflex, or reflex activity, means a spontaneous involuntary event of reaction to a stimulus; this phenomenon seems similar to rapid cellular response events. In the process of creation or perception of reflex activity, the presence of a certain form of sensitivity (or receptiveness) in a system is needed. In particular, this means that in the cellular process, these reactions are realized with the help of mechanosensing.^[10] Mechanical force is essential for the process of mechanotransduction, wherein the cells convert mechanical stimuli or forces into biological signals to affect their behavior. This paper explores the various signaling pathways and methods used in the field of theranostics.^[11] This system works through two interacting phases: the forward phase and the backward (response) phase. These two phases together account for changes taking place in the system. The concept of forward-backward relationship can be defined as comparing the perception of the mechanical force and the response of the cell, which helps to restore or maintain the symmetry (homeostasis) in the cellular environment. Thus, mechanical forces initiate changes, making use of the mechanosensors, that control the cellular processes.^[12] Mechanosensors are found in lipid bilayers, with one end available for pulling and the other surrounded by extracellular matrices or the cytoskeleton. The lipid bilayers vibrate during these activities.^[13] It is vital to discover which molecules detect shifts in the surrounding cell environment to understand how they initiate downstream chemical reactions. These reactions are critical in the context of both preventive therapies and regenerative therapies. The accompanying diagram shows how both the chemical signals and mechanical processes move together to bring about these cellular changes. There are both internal and external nature factors causing increase in the mechanical strain in the cell environment and triggering the cytoskeleton, which will continue these signaling processes.^[14] Interactions between various processes can affect cellular signaling, necessitating careful examination of changes in cell functioning. The author emphasizes the complexity of mechanotransduction mechanisms, which modify cell behavior and maintain homeostasis through different stresses.^[11] Research presents this issue as a primarily multicellular issue and indicates that cell adhesions play a crucial part in transforming mechanical forces into biochemical signals. In multicellular setups, cell-cell or cell-matrix adhesion complexes are of huge importance when it comes to tissue integrity maintenance and tissue healing processes as well. These adhesion complexes are responsible for distributing mechanical strain along the ECM and, consequently, for shaping the cells' ability to sense and react to different mechanical events.^[15] Mechanotransduction pathways in the cell's micro-environment play an integral role in controlling basic functions of the cell, such as survival, shape, and movement. It is crucial to comprehend these pathways correctly to discover

effective preventive and regenerative methods of treatment. Subsequently, the knowledge can be applied for the creation of nanotechnologies.^[16] Investigating how multicellular tissues react to mechanical stressors and understand the flow of information between cells is necessary. In designing and utilizing nanoscale theranostic devices, one has to bear in mind the principles of mechanosensing that affect all processes.^[17] Thus, redesigning these tools to accommodate multicellular assemblies is required. In such assemblies, when intercellular communication is affected, the result is changes that interfere with the normal functioning of cells. This disturbance affects essential processes such as cell polarization, differentiation, junction remodeling, migration, intercalation, and extrusion.^[18] To further the progress in the field of preventive and regenerative treatments, it is essential that certain key scientific questions be solved. Research areas that must be addressed include how cells detect and handle the mechanical forces of neighboring cells, how they react to those forces, and how they transform them into biochemical stimuli.^[19] Mechanical sensors perceive mechanical forces and correlate structural alterations involved in this process, transducing these changes into biochemical signals for mediation of the interactions between cells and with the extra-cellular matrix (ECM), thus initiating a cascade of several downstream signaling mechanisms. In mechanosensitive ion channels, mechanical forces induce conformational changes participating in the opening of the channel and initiating the action of downstream enzymes, which represent the basis of cell signaling according to the tethered model of mechanotransduction (Fig. 1).^[20]

The lipid bilayer model elaborates on the conversion of mechanical forces applied to cell membranes into biological signals by means of force-induced conformational changes in the proteins that are embedded in the membrane. If the biochemical process is not properly regulated, then abnormal deposition of extracellular matrix proteins occurs, which makes any progress toward the field of preventive and regenerative medicine very challenging.^[21] It is thought that aging diseases and other major diseases are caused by the dysfunction of cellular mechanosensing. This malfunction leads to destruction of cells and tissue, which makes it impossible for new tissue to grow and damages healthy tissues. True function of cells depends on their ability to detect and interpret the mechanical surroundings. When this mechanism does not function properly, it means that ion channels cannot be controlled. The primary factors that may lead to the development of illnesses are cells' capacity to respond to biochemical signals and act in response to changes in the extracellular matrix.

In multicellular environments, adherens junctions use cadherin proteins for cell-cell adhesion. These proteins bind to catenin, initiating processes involving filamentous actin for

cell structure support. This sequence continues to operate until it activates the adapter protein catenin, which then brings vinculin into the complex.^[22] Their signaling pathways are maintained until new mechanical links are created among adhesion proteins of the neighboring cells. The cadherin-catenin complex makes the assembly more dynamic. The function of catenins is significant for the operation of the cadherin-catenin adhesive complex, since they respond to mechanical stimuli that impact the intensity, as well as the stability, of protein interactions in the complex.^[23] In the absence of such mechanical responses, cell structures can become susceptible to deformation. The process of wound healing consists of four key stages, which overlap with one another. Chronic wounds result from disrupted healing involving cytokines, growth factors, and the JAK/STAT pathway, with traditional treatments often failing; this review explores the roles of PBM therapy, Wnt signaling in stem cell regulation, wound healing, fibrosis, and potential therapeutic strategies targeting these pathways (Fig. 2). It also points out the new methods to treat fibrotic conditions and the obstacles in this area like the decrease of stem cells availability or their decreased self-renewal capability connected with aging and cell stress.^[24]

Modulating Wnt signaling may support tissue damage repair, given its central role in regulating stem cell activity throughout the healing process. However, precise control of Wnt signaling is essential to prevent adverse effects. This review emphasizes recent findings on Wnt's involvement in reducing inflammation, mobilizing stem cells, and regulating programmed cell death (apoptosis).^[25] These results lead to the design of therapeutic treatment methods based on Wnt for tissue restoration and new-generation wound management. The understanding of the molecular mechanisms behind the activities and adhesion of cells will play an important role in the development of new preventive and regenerative treatment techniques.^[26] The current literature on mechanotransduction, signaling pathways, and mechanosensing is reviewed by the authors. The authors describe how cardiac muscle cells react to mechanical load, with a focus on the structural and functional modifications resulting from metabolic processes in the heart. This section answers some of the questions raised earlier in the literature.^[27] This reaction acts as a short-term adaptation to the initial change in the mechanical load. Still, long-lasting stress can harm the heart and contribute to hypertrophy and heart failure.

Research on stem cells has great potential for solving problems connected with both heart and cartilage by using mesenchymal stem cells. The present study is aimed at analyzing the function of MSCs in mechanotransduction and development of cardiomyocytes and their potential for use in tissue engineering and treatment of heart diseases.^[28] The ability of endothelial cells to detect blood flow forces is incredible, as

Cellular Mechanotransduction and Intracellular Signaling Pathways in Wound Healing: Current Insights and Emerging Perspectives

Mechanical Forces • Cytoskeletal Dynamics • Gene Expression
Mechanisms of Fibroblast Activation and Wound Repair

1. MECHANICAL CUES

Tissue injury creates mechanical tension, matrix stiffness, and compressive forces that are cared by cells.

2. PREGACETION & TRANSMISSION

Integrins and cadherins sense mechanical signals and transmit them across the cell membrane.

3. CYTOSKELETAL DYNAMICS

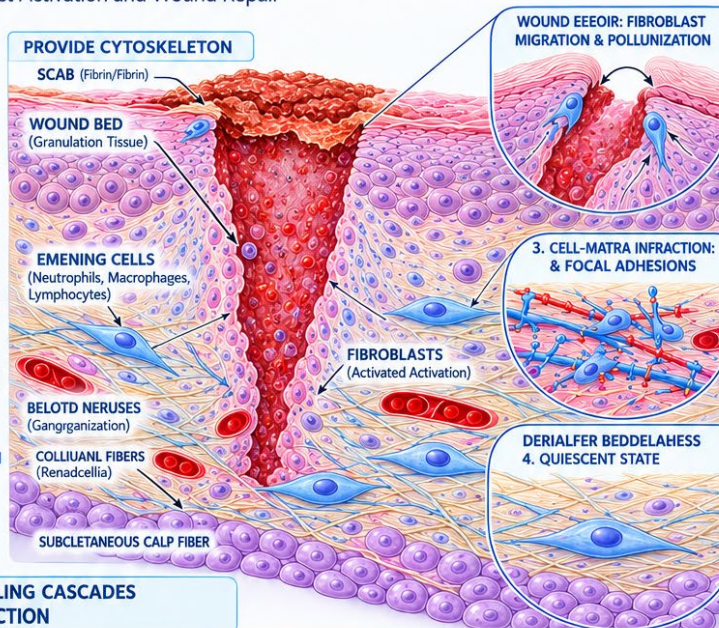
Actin cytoskeleton remodels in transmission, enabling cell contraction, migration, and mechanical reorganization.

4. SIGNALING CASCADES

Intracellular pathways including Rho/ROCK, and MAPK are activated to drive cellular responses.

5. GENE EXPRESSION & FUNCTION

Mechanoregulated gene expression (e.g., YAP/TAZ, RUNX2) produces fibroblast activation, proliferation, and ECM production.



INTRACELLULAR SIGNALING CASCADES IN MECHANOTRANSDUCTION

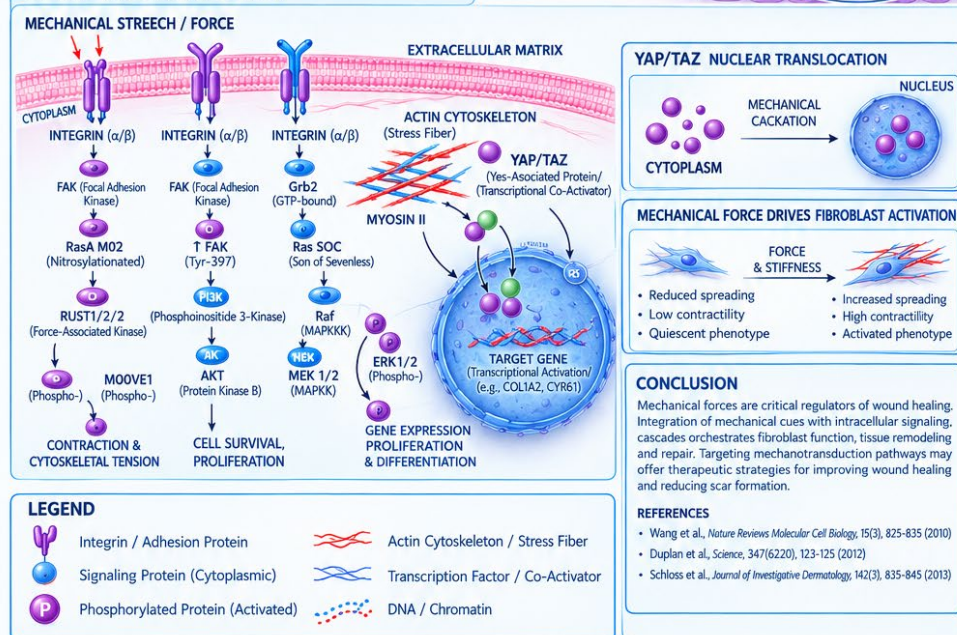


Figure 1. Cellular Mechanotransduction and Intracellular Signaling Pathways in Wound Healing: Current Insights and Emerging Perspectives. Schematic representation of the major mechanotransduction mechanisms involved in wound repair, illustrating how mechanical forces, extracellular matrix (ECM) stiffness, and cell-matrix interactions are sensed through integrins and focal adhesions and transmitted to the cytoskeleton. These mechanical cues activate intracellular signaling pathways, including FAK, PI3K/AKT, Rho/ROCK, and MAPK/ERK cascades, leading to cytoskeletal remodeling, cell migration, proliferation, differentiation, and fibroblast activation. Mechanical regulation of YAP/TAZ nuclear translocation further influences mechanosensitive gene expression and ECM production. Collectively, these pathways coordinate cellular responses, tissue remodeling, and wound closure, highlighting mechanotransduction as an important interface between mechanical stimuli and intracellular signaling during tissue repair.

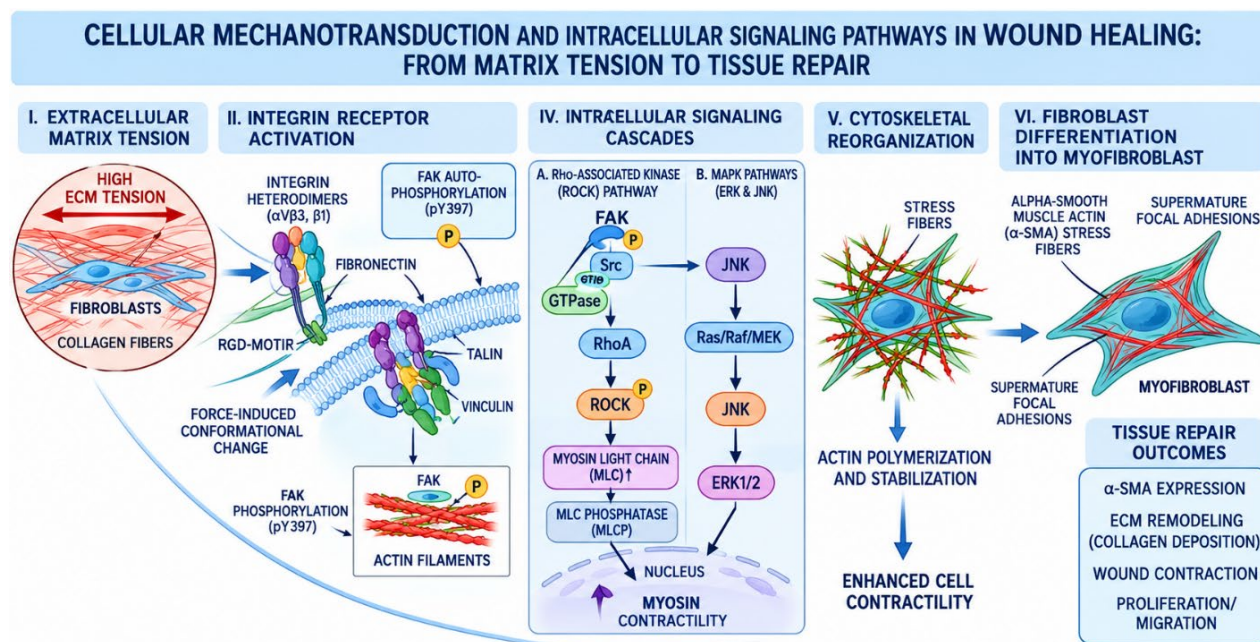


Figure 2. The mechanobiology of wound healing: current trends and future directions. Diagrammatic representation of how the mechanical stimuli acting in the wound microenvironment are detected by the cells and translated through sensor molecules located at the membrane of the cell such as integrins and ion channels. This process results in the activation of intracellular signaling pathways that work together to control the movement cycle of the cell including migration, growth, maturation, response to injury, and generation of new tissues.

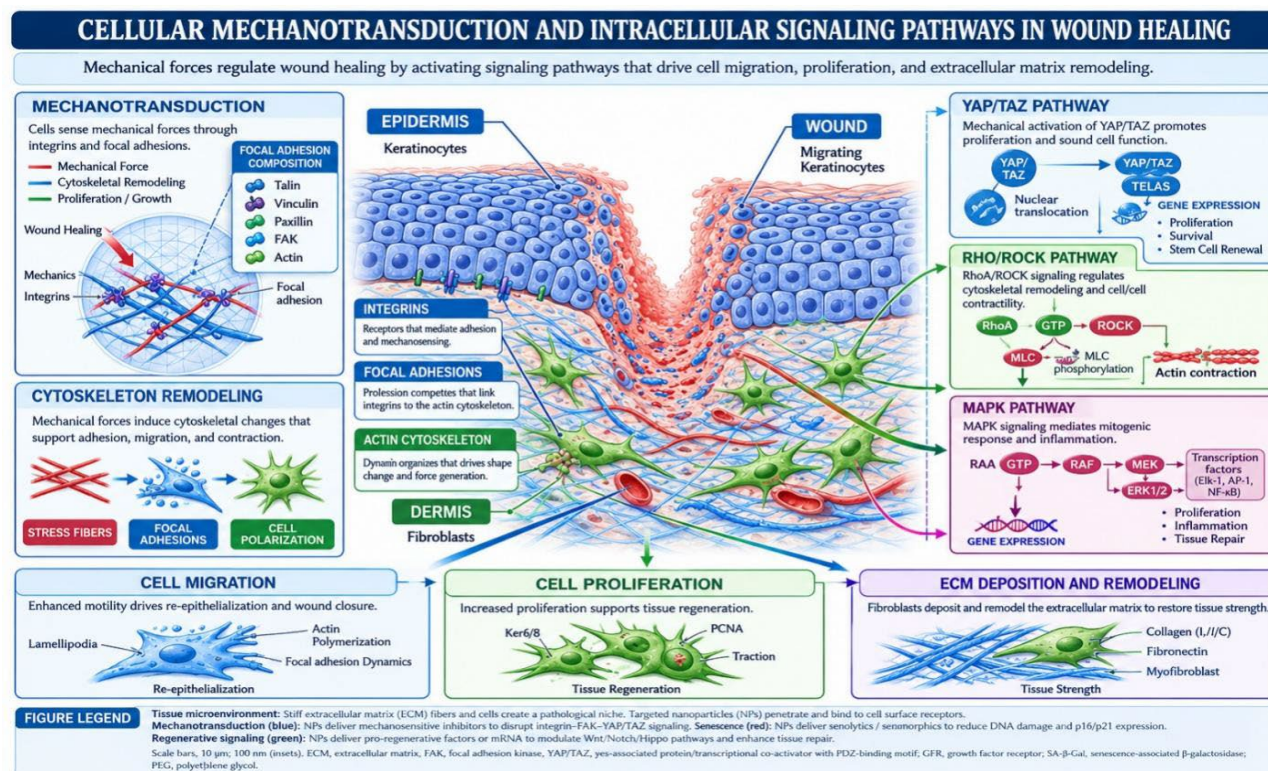


Figure 3. Cellular mechanotransduction and intracellular signaling in wound healing: current insights and emerging perspectives.

they are known for turning physical stress from fluid and pressure into a series of chemical reactions and signals related to blood vessels. Once communication happens from this chemical reaction process, kinases are able to activate initiation of cellular oxidation and modification of the amount of voltage across cellular membrane. This oxidation process leads to activation of an inflammatory signal pathway. It becomes feasible to use nylon technologies for stopping this illness development.^[29] Endothelial mechanotransduction pathways will be modulated for therapeutic reasons using nanoscale devices. Inflammation leads to vasoconstriction and high oxidant concentration in blood vessels. Investigation into the mechanism reveals the effect of inflammation on these signaling pathways and downstream events.^[30] The results of this study may have considerable implications for the advancement of preventive and regenerative treatments for wounds and tissue repair (Fig. 3). The inflammatory response caused by mechanical stress on the endothelial cells of the vasculature represents the initial step in the development of diseases.

New nanodevices must focus on these cellular processes to be effective in healing. Cells operate in complex environments.^[31] The role of cellular response to mechanical stimuli is crucial to preserve homeostasis and influence the development of multiple pathological conditions. Knowledge about the translation of mechanical stimuli into biochemical responses offers promising strategies for improving bone strength, cardiac function, cartilage development, and the design of artificial organs. This article summarizes the principles of mechanotransduction, approaches applicable in experiments involving mechanical stimulation of cells, and some insights derived from experiments exploiting targeted mechanical stimulation of cells.^[14] Mechanotransduction refers to the process through which living cells convert mechanical signals from the extracellular matrix or from the cells surrounding them into biological responses. This process is important in tissue development and in age-associated diseases. Recent studies have indicated that mechanotransduction modulates vital cellular processes such as proliferation, migration, and differentiation.^[32] Accordingly, a deeper understanding of these cellular events is essential and will directly inform the design of novel regenerative nanotherapeutics.

From Signals to Solutions: Integrating Mechanotransduction Cues into Nanotherapeutic Design

Physical forces play an essential role in the physiological processes whereby cells and tissues utilize mechanotransduction to convert the mechanical signals from the environment into biochemical results. This physical communication is accomplished through the combined action of the cytoskeleton, cell-matrix adhesion molecules, extracellular matrix, and also through the cell membrane, which links the cell to its environment.^[33] Recent findings emphasize the significance of the

role of protein unfolding caused by mechanical action being one of the main mechanisms of mechanotransduction. Researchers now continue their work to discover mechanotransduction pathways, with the purpose to explore nanoscale mechanisms allowing to direct the functioning of the cells.^[12] Achieving this goal would require nanofabrication an innovative technology focused on designing tools at the nanoscale in order to create an environment that can directly activate the ECM. At the very least, these developments will be instrumental in controlling the activity of cells and developing nanotherapeutics that provide a working mechanism for interaction.^[34] Cells are structurally complicated in nature and composition, which makes it difficult to carry out their thorough characterization. However, advanced nanoscale techniques are now widely used by the researchers in the study and manipulation of cells in accordance with single-molecule resolution.^[35] These techniques are used to create materials designed as nanodevices and nanotools that represent the cell-matrix interface of cells, allowing the study of the cellular environment. Nanoscale devices and three-dimensional microporous scaffolds can reveal some unexpected details about the components of the cell and their functions, as well as detect the property of the cell surface.

To appropriately guide the actions taken by cells at the nanoscale, it is important to study the parts of cells and their connections. Attention must be devoted to the three aspects of cell behavior: adhesion, signaling, and biochemical functionalization, which might help to find new unknown processes. These three aspects working together affect cells 'action. In this regard, biomimetic scaffolds are used to study the interactions between cells with each other or with their environment concerning angiogenesis.^[36] The major difficulties are connected with drug development and fluid movement in the cellular system. The methods of high-resolution imaging and biomimetic templates make it possible to measure these issues. The assessment of the interfaces created by the cell and new materials is essential to determine how to overcome the problems of manipulation of cells.^[37] Important aspects to investigate include nanotopography, intracellular events, cell pathways, cellular dynamics, mechanosensing, and adherens junctions to comprehend cell functions and care methods.^[38] Nanotopographical machines, such as nanotools and nanodevices, aid in designing strategies to control cell behavior by recognizing physical and chemical signals that manage cell activity and signaling pathways.^[4] Nanotechnology is credited for creating advanced devices that effectively identify and manage stimuli-responsive interfaces, regulating extracellular cues through intracellular sensing.^[39] The development of nanoengineered cell-nanomaterial interfaces and understanding cellular mechanisms will create significant opportunities for precise bioimaging, diagnostics, and therapies in regenerative medicine.^[40] Recent

research indicates that bold ideas about nanotechnology may soon come true. Studies show that devices with nanometer-size structures may affect the functioning of cells. However, more studies are needed to know the response of cells and tissues to these nanodevices, which can confirm their usefulness in biomedical sciences. If nanomachines and nanotools prove effective in regenerative therapy, they can become an important option in regenerative medicine.^[41] Nanoscale tools and devices enable direct interrogation of cellular behavior and the molecular processes that underlie it. Nanoprobes make it possible to visualize and quantify the chemical and biological cues that regulate cell migration, proliferation, and function (Fig. 4).^[42] The results influence a better way to deliver drugs, useful for making regenerative medicines that help cells regenerate and heal. The interaction between cells and nanoparticles improves biological functions. Recent research on neuroblastoma cells used gold surfaces with different roughness levels for regeneration as supporting evidence.^[43] Neuronal sensing responds to nanotopography surfaces and aids in regeneration. Scaffolding materials must mimic cellular environments and cues.^[44] Gold nanoparticles in scaffolds improve stem cell growth and change cell adhesion and signaling.^[45] Nanoroughness surfaces during cell adhesion processes can cause neurons to lose their polarity, and their roughness levels are interrelated to necrosis and cell death pro-

cesses.^[46] Their presence does not significantly affect cell organelles or mechanisms like nuclear condensation and Golgi apparatus fragmentation. Nanodevices and nanotools' surface topography controls cell behavior. Cells specifically adhered and functioned only on flat gold stripes, promoting precise biological reactions from nanostructures.^[47] Key mechanisms and pathways, such as motility, differentiation, proliferation, apoptosis, and mutations, were identified through intracellular and extracellular mechanisms.

Nanotools and nanodevices enabled detailed studies at the single-cell level.^[48] Both in vitro and in vivo applications involve the use of nanodevices and nanotools to facilitate the imaging of tissues and cells. Studies show that mechanosensors within the cell can convert mechanical signals into biological signals. Using mechanical vibrations to create mechanotransduction pathways can thus allow for the manipulation of cell behavior without the use of drugs.^[49] The novel use of technology involving nanoscale sinusoidal vibration has great potential for drug discovery, clinical tissue engineering, and regenerative therapeutics. This method, referred to as nanovibrational stimulation or "nanokicking," as it is commonly called has been particularly useful for promoting cell and tissue regeneration.^[11] Soft gel structures activate processes and signaling pathways important for detecting cell differentiation.

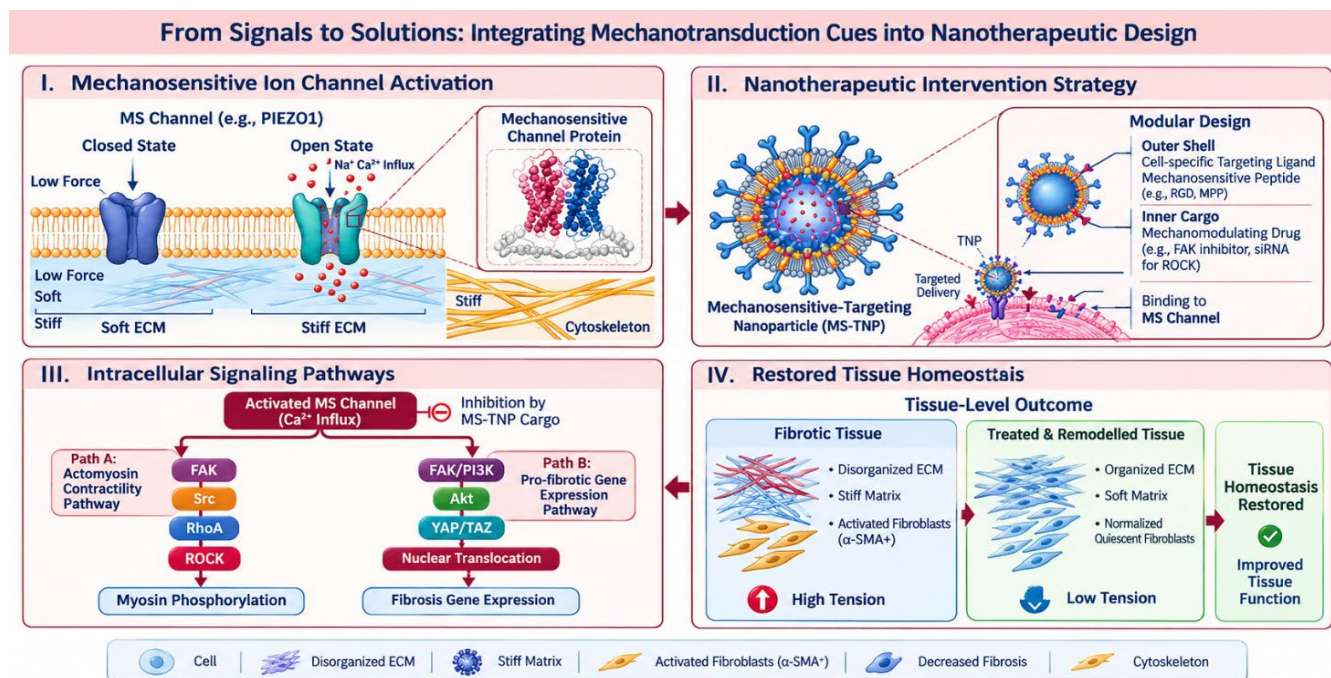


Figure 4. From Signals to Solutions: Integrating Mechanotransduction Cues into Nanotherapeutic Design. Schematic illustration of a mechanotransduction-guided nanotherapeutic strategy, showing (I) mechanosensitive ion-channel activation in response to extracellular matrix stiffness and mechanical force, (II) targeted delivery of a modular mechanosensitive nanoparticle, (III) modulation of intracellular FAK/Src/RhoA/ROCK and PI3K/AKT/YAP/TAZ signaling pathways, and (IV) subsequent remodeling of the fibrotic microenvironment toward normalized tissue architecture, reduced mechanical tension, and restoration of tissue homeostasis.

Clinically relevant osteoblast volumes are used for bone grafting.^[50] Initial studies show that the usage of nanovibrational stimulation technique does not cause biofilm development when bacteria is present. This is a positive result, which describes the effectiveness of such techniques in experiments where it is important to ensure that the background is biologically inert and all determined effects can be attributed to the bioactive ligands only, without any influence from specifics of the proposed platform.

Mechanosensor Network: Nanotherapeutic Strategies to Overcome Signaling Defects

Mechanobiology studies the influence of physical and mechanical factors on cells, especially stem cells. Findings in this area indicate that properties of their environment and 3D structures impact cell movement, development, and other reactions. In this review, we cover the basic aspects of stem cell biology along with an overview of current mechanobiology publications.^[51] The objective is to investigate various techniques employed to simulate these mechanical factors in order to enhance their implementation in regenerative medicine. Regenerative therapy is based on the idea of healing damaged tissues, organs, and cells; and when healing is not sufficient, the regenerative process of creating tissues takes place. The purpose of this kind of treatment is to recover the ordinary structure and functioning of a damaged tissue. Simultaneously, the field of nanotechnology contributes to the solution of existing problems related to the creation of nanotechnology products.^[52] Nanotechnology-based methods, termed nanotherapeutics, have the potential to enhance tissue and cell regeneration. When functioning on a nano level, these methods allow cells to recognize and rectify abnormalities in their functioning. Nanotechnology has been used in medicine in many ways, including in drug delivery, cellular visualization, support of tissue engineering with nutrient-supporting scaffolds, and in improving the functions of stem cells.^[53] The best sources for developing regenerative treatments are multifunctional nanomaterials and fabrication processes. They are used to treat bone, neural, muscle, and cardiovascular diseases.^[54] Nanomaterials and nanobiomaterials may kick start regenerative processes in order to enable repair of normal cell and tissue activities in conjunction with the application of such materials and tools. Many chronic wounds and injuries remain difficult to treat using classical methods; however, the nanotechnology may allow for new possibilities of treatment, including nanodevices. In fact, the nanotechnology is becoming a leading treatment method in the field of wound treatment as well as the creation of new healing methods.^[55] The phase of research will concentrate on generating replacement for organs like liver, kidney, heart, and skin through methods including applications of nanofabrication, microfluidics, nanobiotechnology, and artificial organs. As long as nanotechnology develops further, it is pos-

sible to support current medical approaches as advanced scaffolding is about to become more effective in terms of tissue engineering.^[56]

Tiny tools and gadgets can enhance cell adhesion and growth by providing a network of surface molecules. These outcomes will change different aspects of regenerative therapies. The new scaffolds have a three-dimensional structure and mimic the extracellular matrix.^[27] Therefore, one of the current trends and potential applications for nanocomposites in cell and tissue regeneration is their biocompatibility and lack of toxicity.^[46] The extracellular matrix (ECM) is extremely important in terms of tissue repair and tissue health. It provides the structural and biochemical support for tissues, helping them to protect against infections and disease processes. Once any damage occurs, tissue-healing needs to start immediately in order to maintain the functioning of the cells. A key to this is the communication between cells and the ECM, and any disruption in this communication will prevent the normal functioning of cells. Thus, careful examination of the processes involved in this matter is essential for designing new methods in the area of tissue engineering.^[57] Nanomaterials are crucial in improving cellular defense mechanisms and regulating signaling systems necessary for cell operations. The main purpose of their use is to recover damaged elements, such as blood arteries, the heart, and the lungs with the help of tissue engineering, preventive therapies, and regenerative medicine. Tissue engineering aims at restoring defective cells, tissues, and organs.^[3] Two types of challenges related to regenerative treatment from a medical perspective can be found in literature.

In this context, the role of nanotechnology as a perfect means for ensuring cellular mimicry, simulating cellular communication, and enhancing cell and tissue regeneration cannot be underestimated. This review aims at highlighting the newest developments in the area of regenerative medicine to identify some key problems. The idea is to utilize advanced nanoscale scaffolds to restore or replace damaged cells, tissues, and organs that can be considered the basis of effective regenerative treatment. However, it is worth noting that the success of these techniques in managing cells will depend on the implementation of specific nanotechnology-based approaches.^[58] It discusses the operations in nanoscale devices and their role in investigating the interaction of cells with their surroundings. In addition, it mentions the technology of scaffolds applied to tissue engineering and various fields such as neurology and cardiology. It reveals that damage to the spinal cord causes the interruption of neurons that prevents the regeneration of tissues.^[59] The combination of regenerative medicine and regenerative nanotechnology can lead to greater efficacy. When used for targeted delivery in areas of damage, nanodevices are capable of decreasing the degree of cell death and inflammation while supporting

important healing processes, including angiogenesis and neuroregeneration.^[60] Nanodevices can be used in many fields of regenerative medicine such as diagnostics, drug delivery, cell therapy, and tissue engineering. Graphene-derived materials play a major role in the process of producing biocompatible scaffolds for tissue regeneration purposes. Their multifunctionality enables the creation of 3D graphene scaffolding very close to natural processes which positively expands their use in therapeutic procedures, like cellular differentiations and drug discoveries.^[61] The materials used in 3D scaffolds like collagen and silk fibroin affect their biocompatibility because of their composition and method of production. These scaffolds assist in recreating the endothelial matrix and maintaining the function of the cells via enhancement of the physical and chemical microenvironment.^[62] 3D scaffolds provide capabilities for drug delivery and act analogously to natural processes of regeneration. Their size at nanoscale allows for proper interaction of cells with ECM. Therefore, they play an important role in regenerative medicine because of their properties. ECM consists of structural constituents whose size correlates closely with that of these

devices and therefore can be easily combined with them. These devices can change cell behavior and assist drug delivery and hence are important in scaffold construction for the purposes of tissue engineering and improvement of the state of cell damage as well as tissue formation and inhibition of abnormal activity of cells (Fig. 5).

Cell senescence is the process that takes place under the influence of different stimuli such as telomere shortening or oxidative stress.^[63] Cellular senescence has a crucial role in various health disorders and plays a vital part in age advancement and life expectancy. Scientists are conducting researches to discover the principles regulating cellular senescence, the latest studies revealing that the calcium signaling process might significantly contribute to this phenomenon. The article will explain how calcium signaling is related to the cellular senescence process.^[64] Cellular senescence is caused by telomere shortening, oncogene activation, and oxidative or genotoxic stress.^[65] The text emphasizes calcium's role in survival, wound healing, embryonic development, and aging, noting high levels in aging cells and relevant proteins.

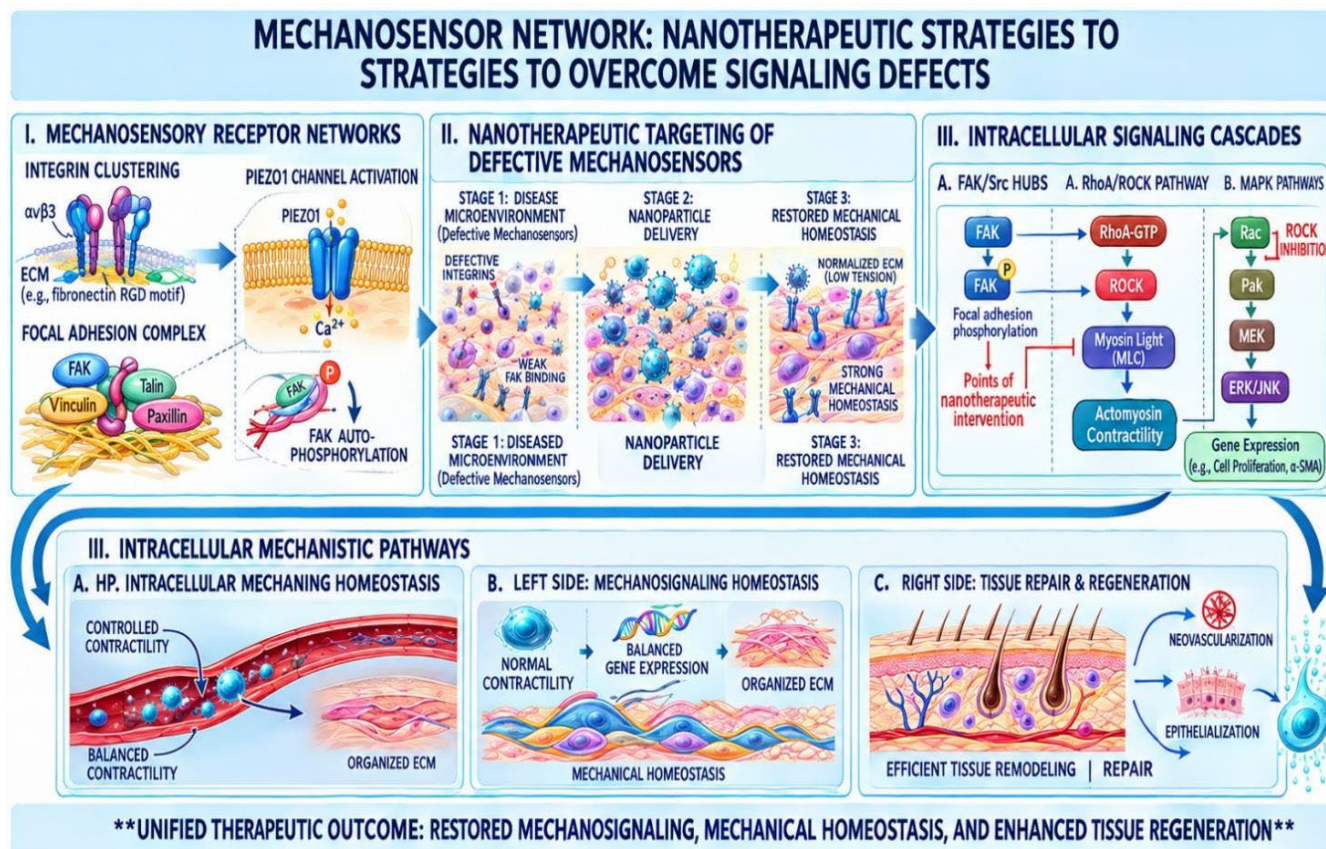


Figure 5. Mechanosensor networks and nanotherapeutic strategies for overcoming signaling defects.

The Role Nanotherapeutic Platforms in Mechanobiological Regulation and Mechanotransduction Pathways

Scientists study mechanotransduction by applying mechanical stresses like stretching, pressure, compression, and shear to cells, along with exploring effects of vibrational stimulation.^[66] Though these techniques lead to the discovery of downstream events related to the expression of genes, modification of cell shape, and the localization of proteins, they do not elucidate the upstream mechanisms by which cells perceive mechanical stress and convert it to changes in gene expression.^[67] Studies show that mechanical energy can actuate proteins in a direct manner that involves conformational change. For example, Piezo ion channels behave like mechanical levers, their opening being triggered by tension applied to the membrane; besides, the structure of filamin A adapts to the mechanical forces exerted during muscle contraction in order to reveal a hidden site for binding. Similar to that, R8 domain (the 8th rod domain) of talin starts unfolding and gives rise to signaling pathways when being exposed to mechanical force.^[68]

Shearing stress can change the shape of the von Willebrand factor so that its binding regions become accessible for receptors. Likewise, sonic waves can cause the opening of Ca^{2+} channels within the inner ear hair cells. The results were based on a clear cutting-edge structural study indicating the need for advanced nanotechnologies that can detect biological molecules' conformational changes while keeping them intact and its biological role preserved. Mechanical forces can be transmitted via several processes including fluid movement and cytoskeleton. The cytoskeleton is said to be very adept at transmitting forces over long distances; it connects to the LINC complex (Linker of Nucleoskeleton and Cytoskeleton) and is responsible for regulating gene expression by passing mechanical signals onto the nucleus. The identification of proteins transmitting force may take place using various methods, including the disturbance of the cytoskeleton the use of CRISPR screening and the resulting real-time observation thanks to fluorescent markers.

Mechanotransduction channels are responsible for changing mechanical signals into biochemical signals, allowing ions to enter the cell. When exposed to mechanical force filamin A connects to integrin, misfiling and other proteins interacting with FilGAP, which results in the separation of FilGAP from the given complex. It affects cell adhesion and movement although it is still unclear what function much of this related proteins have. FilGAP is responsible for the guiding of filamin A towards the membranes and adjusting the cytoskeleton.^[69] Though numerous molecules are implicated in mechanotransduction, there is insufficient understanding of the exact processes involved in transforming mechanical forces into chemical signals. To support the progress in the study of

the field, accurate evaluations of the force in action in the tissue and cells are needed. The stiffness and viscosity values reported can be quite different based on the measurement method. For instance, the elastic and viscous properties of MCF-7 breast cancer cells can vary from one study to another. Likewise, folding or unfolding a protein is also dependent on the method applied; even the unfolding force varies by the force applied and the rate of loading.

Measurement methods such as atomic force microscopy (AFM) and magnetic tweezers may give different outcomes as they provide different experimental conditions. In this case, nanotechnology is utilized for the mechanical control of molecules. In particular, magnetic nanoparticles (NPs) are employed for activation of the signaling pathways, steering of the differentiation of stem cells, performance of targeted killing of tumorous cells, and treatment of diseases affecting the nervous system. Nanoparticles (NPs) vary in different sizes and they are usually taken in cells. Magnetic micropillar surfaces assist in mechanotransduction-related investigations in which mechanical effect can be applied to cells. Optical and magnetic tweezers are also applied to held particles and connect them to some substances needed for applying or measuring forces. Atomic force microscopy (AFM) enables the imaging and manipulation of single molecules, with high-speed AFM able to quickly record biological actions.

Mechanotransduction is key for tissue development and repair, which is difficult to replicate in tissue engineering. Tailored nanomaterials can assist in this process, guiding stem cells into specific cell types and enhancing the growth of muscle and nerve cells.^[70] The addition of nanoparticles can improve the effectiveness of hydrogels that serve as tissue scaffolding in tissue engineering processes. In the field of nanomedicine, cellular absorption of nanoparticles depends to a large extent on the mechanical properties of the particles, including their rigidity and elastic properties.^[71] There are key differences between healthy and diseased cells, suggesting that targeting NPs based on mechanics could be helpful.^[72] Magnetic nanoparticles are able to trigger specific processes from a distance, thus enhancing bone health and cognitive processes.^[73] Other types of materials, including carbon nanotubes, can likewise support tissue engineering and cell growth. However, thorough safety assessments of all nanomaterials is needed before they can fully enter the sphere of medicine and human healthcare. This portion of research progresses further: scientists must shift from the level of basic mechanobiology to the field of technology used in healthcare. For example, the development of novel therapies aimed at the mechanical parameters related to solid tumors occurs, as these factors can be responsible for the response of tumor loco-regional cells to therapy, such as interstitial fluid movement and the tissue structures of neoplasms.

Current research explores combined therapies targeting tumor mechanics and treatment, with mechanobiology methods used to improve diagnostics by identifying mechanical differences, such as stiffness and adhesion, between metastasized and non-metastasized cancer cells for potential disease markers. Future studies will look into how different types of cells within the tumor have different mechanical qualities, and how it connects to their particular invasive and metastatic abilities. The creation of these relationships could enable the use of single-cell mechanophenotyping as an effective and dependable diagnostic method. At the same time, scientists are exploiting mechanobiology in combination with AI, employing biosensors to convert mechanical and physiological modifications into signals that could be used for AI analysis. That is the reason why mechanobiology becomes more and more important in the field of regenerative medicine and tissue engineering creating the basis for a new class of materials known as mechanobiomaterials.^[74] This new field is concerned with how to modify the physical properties of biomaterials to obtain desirable biological responses in order to facilitate tissue repair and regeneration. For example, smart biomaterials can implement tunable mechanical parameters in order to control the differentiation of stem cells or can stimulate tumor cell processes that push them back to normal processes by applying specific mechanical signals (Fig. 6).

In addition, researchers are working on developing the biomaterials that can sense individual cellular requests and adjust their properties accordingly. Such an approach may be especially important in cancer treatment since, for example, a smart material used in the area of tumor resection can identify the presence of tumor cells and change its mechanical characteristics to suppress their invasion.^[76] The study of mechanobiology is progressing quickly, but it still has a long way to go in order to understand its meaning in clinical practice. This shows the need for broader participation in solving these unanswered questions. Nanotechnology, because of its nature, is a combination of different disciplines, namely chemistry, engineering, health science, materials science, biology, and physics. This has changed medicine thanks to advanced possibilities. Nanodrugs and their delivery systems such as nanoparticles, liposomal nanoparticles, and nanohydrogels are now very helpful in regenerative therapies.^[77] In this paper, different classes of nanomaterials that are involved in healing and regenerative medicine have been discussed. Many research studies have been carried out to understand the antimicrobial properties of silver, gold, and their alloys that are synthesized using certain methods. Besides that, advanced hydrogels incorporating gold nanoparticles are introduced as new “smart” wound healing agents that can act upon stimuli. Apart from the above-mentioned metals, different metals, such as cerium oxide, silica, zinc oxide, and

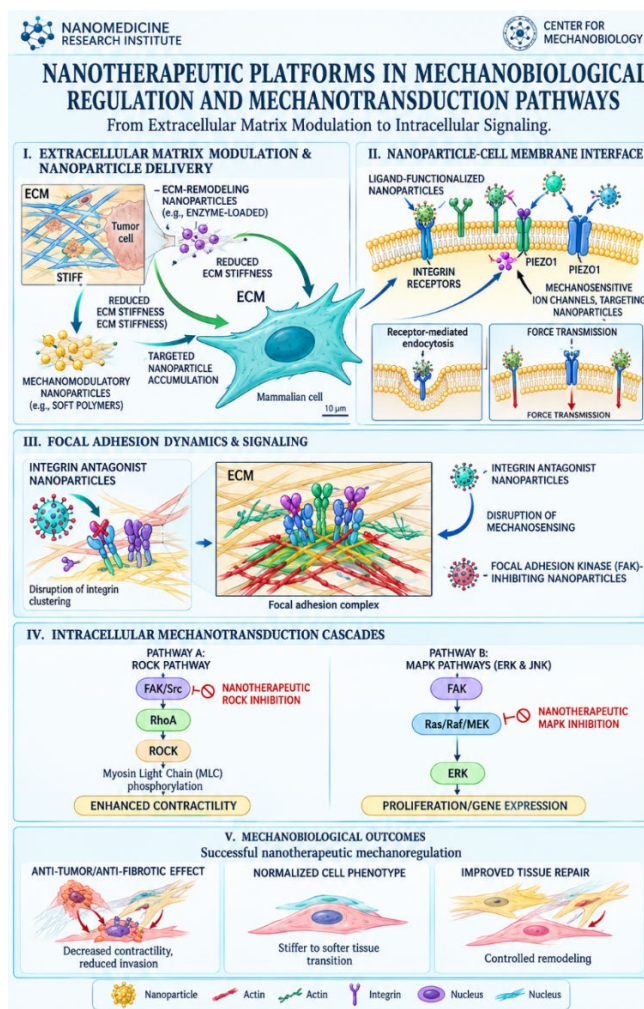


Figure 6. Schematic overview of the focused areas in Frontiers in mechanobiology and mechanomedicine. Reprinted (adapted) with permission from.^[75] Copyright (2023) Springer Nature Limited.

copper, are being investigated. Finally, nanoparticles like graphene and various metal oxides are being discovered as new agents preferred in regenerative medicine.^[78] Different forms of nanoparticles such as bioactive glass nanoparticles and magnetic nanoparticles have immense potential in wound healing applications. Specialized hydroxyapatite nanoparticles are also able to bind to ions and proteins from their vicinity, contributing to the regulation of calcium content in the wound area and making it possible to facilitate the wound-healing process.^[79] These nanoparticles exhibit strong structural stability and adaptable architectures, making them excellent candidates for improving wound healing outcomes in experimental models. Their built-in therapeutic properties also make them well suited for sustained, long-term medication delivery. The use of nano/biomaterials is significant in tissue engineering and molecular design since they

help in cell growth and development. They act as a bridge between biomedicine and the science of nanomaterials, thus being a vital foundation for preventive and regenerative medicine.^[80] Tissue-engineered scaffolds benefit from the materials that imitate the extracellular matrix, promoting cell adhesion, helping in the delivery of bioactive materials to trigger immune responses. The inclusion of functional ligands aiding in cellular adhesion will further lead to improved healing results.^[81] Surface treatment may create enhanced nano-bio interfaces, and many recent studies suggest that synthetic nano fibers scaffolds could be a viable substitute for natural physiological conditions, improving cell response in self-healing processes. Regenerative nanotherapeutics seeks to use engineered nanoscale materials to leverage the cell's natural repair and defense processes. In order to make advances in therapies development, acquisition of sufficient understanding of the cellular reaction to mechanical influences is required.^[82] This information can lead to enhanced treatment approaches and broaden the usage of nanoscale devices in the healing process. Nonetheless, there are numerous difficulties associated with understanding how cells counteract different mechanical forces and transform them into biochemical signals.^[83] In this role, cadherin plays the important role of being a mechanosensor, and it is important to understand the working of mechanosensors on a larger level to be able to develop treatments. Disturbances in normal cellular processes result in overproduction of ECM proteins and the onset of aging and diseases.^[10] Timely cellular responses to biochemical signals and changes in the extracellular matrix are critical for normal tissue function. For instance, endothelial cells are capable of detecting hemodynamic forces, which in turn can modulate inflammatory signaling pathways. Nanoscale technologies could be applied to control those signaling pathways and prevent disease, thus paving the way for effective therapy in the field of tissue engineering. Cell-cell interactions and interactions between the cell and the ECM play an important role in regular functioning of cells, as any alterations in these processes can lead to drastic modifications in cell behavior.^[84]

Nanotechnology is vital for creating therapies that help regenerate cells and tissues by mimicking how cells work and fixing signaling difficulties.^[84] The method of repairing damaged cells, tissues, and organs relies on advanced nanoscale scaffolds, which help in the process as long as the cell behavior is controlled properly. The agents are responsible for enhancing the cell response needed for drug delivery and regenerative medicine.^[85] Materials that are based on graphene are highly effective scaffolds for the purpose of tissue regeneration and are based on 3D designs that resemble natural cellular processes. The success of the 3D scaffolds can be attributed to their structural design and the ability to improve the cellular microenvironment, helping in key pro-

cesses like drug delivery. In addition, the assistance of AI technology can aid in selecting the best material for the scaffolding processes and lead to a better understanding of diseases and treatment methods. Healing of wounds or injuries is a lengthy process that involves several stages and often requires sophisticated treatments especially in case of severe or chronic types of wounds. Healing of a wound goes through four main stages, namely coagulation (hemostasis), inflammation, proliferation, and remodeling, thus leading to formation of scar tissue. Proper management of wound healing is vital for the outcome of treatment. Different cellular and molecular mechanisms involved in the healing process include inflammatory signaling and formation of blood vessels; therefore, there is a demand for new therapeutic approaches aimed at bettering regenerative abilities. It is necessary to understand the mechanisms of interaction between cells during injury and healing process concerning both the activity of adhesion molecules and cytokines.^[86] The inflammatory phase brings immune cells to aid repair.^[87] Another subject of great interest is the study of mechanical forces and their influence on healing. Skeletal muscle is especially important because of its intrinsic ability to remodel. Calcium signaling is significant in muscle development and repair. Since calcium serves this function, it can be helpful to study its contribution in order to develop better methods to treat diseases related to muscles.^[88] Calcium-related signaling pathways, as indicated by recent findings, characterize the operation of satellite cells and muscle cell formation allowing introducing effective regenerative medicine treatment methodologies. The role of calcium in signaling enables cells to cope with injury-related stress. It is worth mentioning that epithelial cells play a crucial role in the mechanisms of this process influencing various cellular activities such as growth and movement.^[89] Modern techniques, like imaging and modeling, help explain calcium's role in healing. Calcium is also essential for cell movement and regeneration in wounds.^[90] Furthermore, cellular aging affects calcium signaling, impacting disease management and treatment strategies.

Nanotherapeutics Targeting Senescence and Controlling of Regenerative Signaling Networks

The process of telomere shortening takes place during DNA replication due to the problem of end replication. However, if protective properties such as telomerase or telomere recombination are absent, the telomeres keep shortening with every new cell division. Finally, this shortening process results in telomeres becoming critically short and leading to replicative senescence. In the process of replication, ligating the RNA primers from the lagging strand by leaving very short gaps creates single-stranded overhangs on the DNA molecule. The 3' G-rich part of DNA is perceived as damaged DNA by ATM/ATR (ataxia telangiectasia mutated/ATM- and Rad3-related).^[91] The recognition of this phenomenon

causes a chain of events in the damaged DNA pathway and subsequently causes the cells to go into replicative senescence. In those cases, where more advanced telomere dysfunction happens, ATM/ATR becomes able to activate CDKN2A. As a result, the level of p16INK4a increases, and the cycle stops. It is also worth pointing out that oxidative stress accelerates telomere shortening as in diabetes, for instance, it causes telomere damage and diminishes the activity of telomerase rather than accelerating its work. At times this cycle arrest may be reversible, but if things go wrong, then a permanent arrest occurs instead. The telomeres are rapidly getting shorter, thus, they will eventually be seen as damaged DNA, which in normal circumstances is prevented because of the protection of the so-called sheltering complex that covers and protects the length of telomere. When these protective components deteriorate, the resultant unprotected telomeres have the characteristics of double-strand DNA breaks, which trigger a more profound reaction known as DDR. Thus, further experiments should be conducted to investigate whether cellular aging is indeed dependent on DDR

activation. Senescence-related heterochromatin destruction leads to the disturbance of the workings of enzymes that modify histones, with the indicative lowering of the number of the histone lysine methyltransferases SUV39H1 (suppressor of variegation 3-9 homolog 1) and SETDB1 (histone-lysine N-methyltransferase SETDB1) and the rise in the enzyme content, responsible for demethylation action, in particular, KDM4A (lysine demethylase 4A) or KDM4B (lysine demethylase 4B). The absence of heterochromatin protein 1 (HP1) leads to the rapid loss of heterochromatin and the beginning of senescence, while the restoration of HP1 content helps retain the chromatin structure stable and prevents premature (early) senescence.^[92] Various factors, including circadian regulators and sirtuin family members, influence senescence.^[93] Activation of p21 (cyclin-dependent kinase inhibitor 1) causes the temporary and reversible arrest of the cell cycle during the early onset of senescence, while p16 (16-kilodalton protein, scientifically referred to as cyclin-dependent kinase inhibitor 2A) ensures maintenance of senescence in the longer term (Fig. 7).

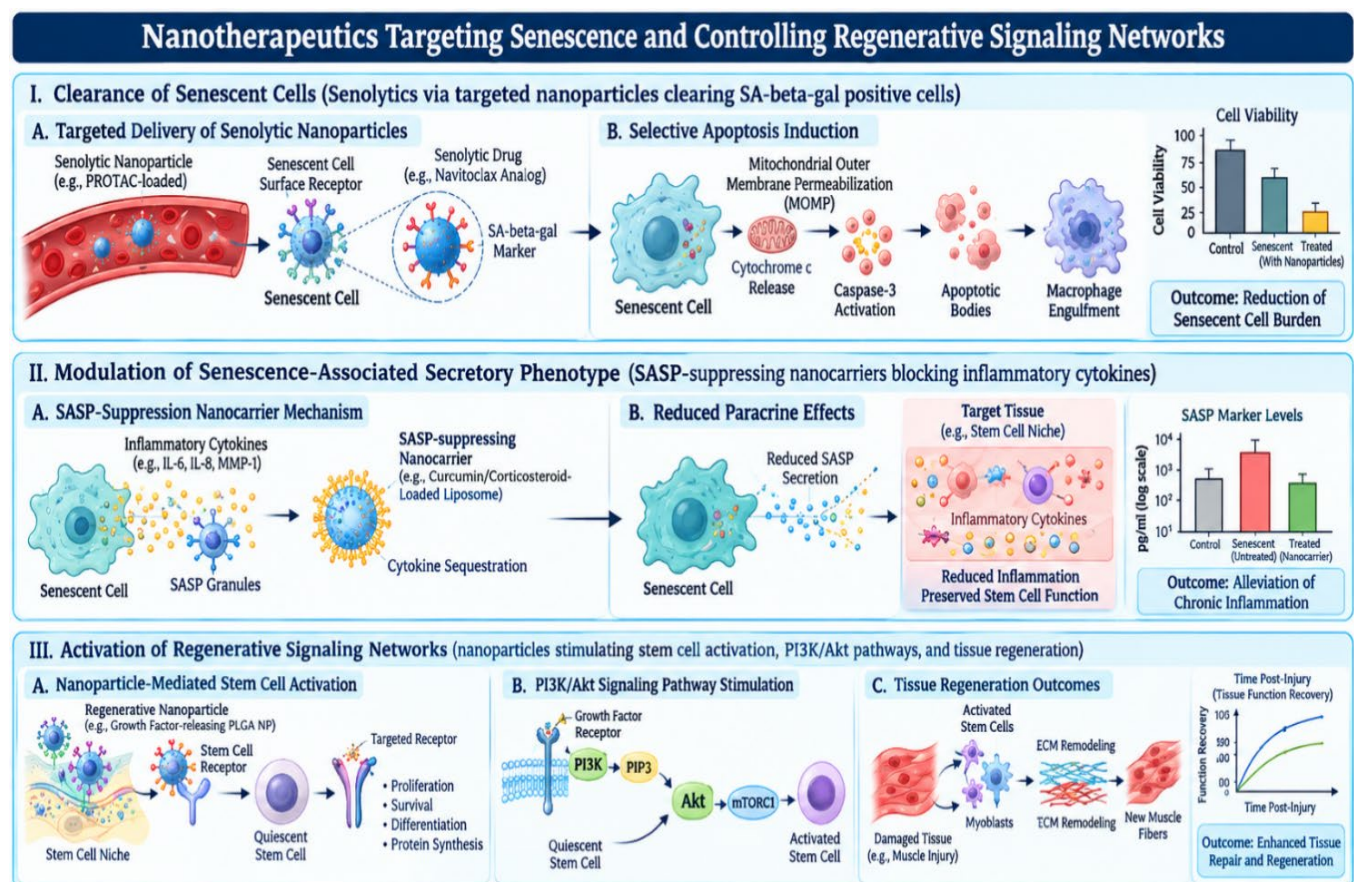


Figure 7. Nanotherapeutics targeting cellular senescence and modulating regenerative signaling networks.

It is necessary to understand these mechanisms in order to invent efficient methods of treatment against aging. Mitochondrial problems have both caused and resulted from cellular senescence, leading to problems related to the increase in DNA damage and changes in the autophagy process. The protein p53 (tumor protein 53) can suppress mitophagy, increasing the heart dysfunction in elderly models, and this can be avoided through stimulation of Parkin or depletion of p53. Changes in pH also negatively impact autophagy, and imbalances in calcium levels disrupt mitochondrial function and energy balance during senescence. Cellular aging is responsible for altering cellular activity significantly, mainly due to the activation of the secretory phenotype associated with cellular aging. The secretory phenotype involves a number of secreted substances that stabilize the state of senescence, modify the microenvironment of the tissue around the cell, and affect the general functioning of the body. Important cytokines such as IL-1 α and IL-1 β stimulate the synthesis of other interleukins such as IL-6 and IL-8 responsible for maintaining cell cycle arrest and regulating immune response. Transforming Growth Factor- β (TGF β) further enhances aging effects and SASP factors. Chronic inflammation accelerates immune cell senescence, worsening aging.^[94] Studies show that the ability to synthesize proteins declines with age, causing issues linked to neurodegenerative diseases.^[95] Issues with the maintenance of proteostasis can lead to many diseases, and approaches boosting the mechanisms of protein quality control may prove useful in therapy.

Immunomodulatory Nanotherapeutics for Wound Healing

More and more researchers are taking an interest in treatment methods based on nanozymes and exosomes because of their biomimetic nature, which gives these compounds properties needed for regulation of reactive oxygen species, regulatory immune responses, and stimulating formation of new blood vessels. The therapies are developed according to sophisticated fabrication methods to ensure their effectiveness and physical stability in body. A great deal of research has been performed on scaffolds, made of silver nanoparticles integrated into collagen-chitosan materials.^[96] These gels show strong adhesive characteristics and release nanoparticle drugs in a controlled way, which helps in achieving sustained therapeutic effects and aid in tissue healing. There are studies suggesting the presence of nanozymes that work like enzymes to replicate the processes taking place in a human body; a rather interesting option. These antibiofilm nanozymes are able to disrupt the biofilm, implement tissue repair and do not even use traditional antibiotics, which is important with regard to emerging issues regarding antibiotic resistance. Furthermore, plant-made exosomes are easily integrated into nanocarrier system and are known to be helpful for promoting angiogenesis, especially in diabetic ulcers,

thus showing promise in this regard.^[97] Moreover, gold nanoparticles made of plant extracts are characterized by antioxidant and anti-inflammatory properties and can be helpful in the process of tissue repair in experimental models. Inflammation has a dual function in health as it not only causes various diseases but also acts as a means for maintaining homeostasis. Nevertheless, inflammation can damage the tissues and trigger the development of chronic inflammatory diseases. Biomimetic nanozymes and exosome therapies are being proactively studied for their capability of modifying inflammation and promoting tissue healing.

Presently, standard treatments such as antibiotics and corticosteroids can only offer temporary relief. Fresh developments in immunomodulation technology, particularly in terms of the use of advanced nanotechnology, seem to provide a more efficient and effective way to regulate inflammation. This article discusses the mechanism of inflammation and existing treatment options, as well as the new trends in the use of nanomedicine for treatment purposes. The problem of chronic wounds is caused primarily by the increase in the elderly population globally. Chronic wounds are usually associated with a disturbed immune microenvironment, which leads to the long-lasting inflammation process.^[98] Although there have been introduced plenty of immunomodulation techniques, the current methods of their introduction do not contribute to proper efficiency. Thus, it is evident that new and more effective advanced delivery systems, including nanotechnology, are badly needed for proper treatment of inflammation.^[99] Research suggests that nanodrugs administered via the nasal route can attenuate allergic response by altering the immune response to allergens in the immune cells. A major aspect of this process is the stimulation of regulatory T cells, which are critical for controlling immune reactivity. If such cells are not sufficiently generated, the immune system will always be in a hyperactive state. Nanodrugs can stimulate their generation and deliver allergens to appropriate immune cells to restore the immune balance. Specifically, their therapeutic action works through several pathways at once.^[100] These are surfaces like the lining of the nose and lungs. Nanodrugs can cross these surfaces. Trigger the right response. This gives a foundation, for future therapies.

To achieve proper wound repair, communication between many different cell types and molecules is needed making this process very complicated? For example, for chronic wounds related to diabetes there seems to be something that contributes to the disruption of this coordination generated by chronic inflammation, toxic substances produced by dysregulated immune system cells and infection.^[101] The creation of new blood vessels is also disturbed and makes the process of healing inefficient. Therefore, we are witnessing a transition from simple dressings to more sophisticated methods aimed at creating proper immune microenvironment and im-

proving healing process. For such an aim, the materials that are used for wound healing are polymers and polymer-based materials that can be customized for wound healing processes and whose function is to influence the immune response so that the immune system behaves as pro-healing.^[102] The current article discusses the complications related to healing process, some design principles used for creating polymer-based materials, and some important aspects of their use in the clinics.

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Future studies should try to understand the healing process inside the wound how M1 and M2 macrophages affect it and how these biomaterials work with inflammation and tissue repair.^[103] If it all works out this research could lead to improvements in managing chronic wounds. Chronic wounds are an issue and M1 macrophages play a key role.^[104] Biomaterials that shift macrophages from M1, to M2 are being explored. M2 macrophages promote healing. Chronic wound healing is the goal.

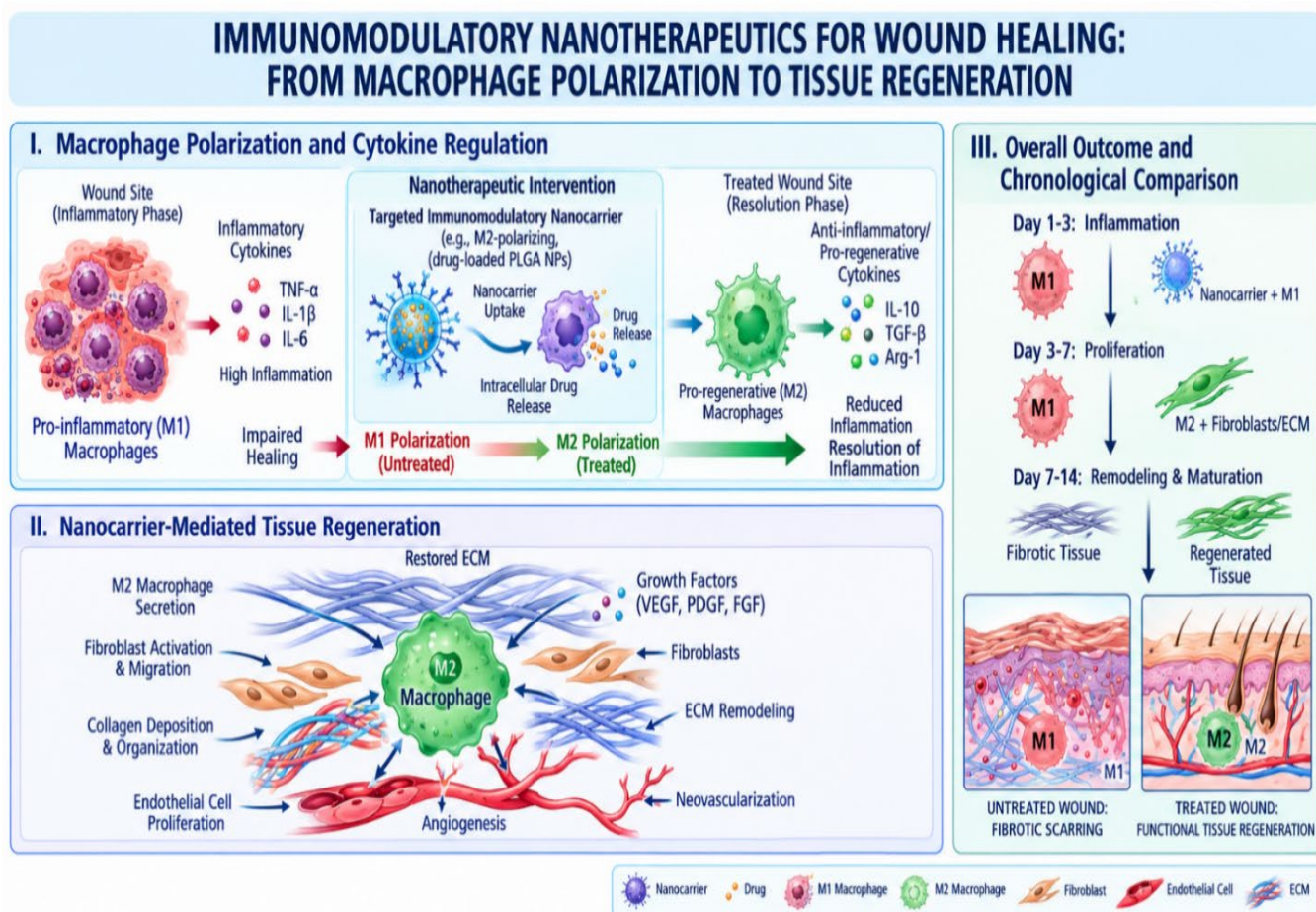


Figure 8. Immunomodulatory nanotherapeutics for wound healing: mechanisms, therapeutic strategies, and emerging perspectives.

Intelligent Nanotherapeutic Systems for Mechanotransduction-Guided Wound Repair

The treatment of patients suffering from cancer is based on a combination of multiple drugs. Whereas earlier treatments mainly used the single-drug concept, researchers now believe that nanomedicine treatment strategies can improve treatment results greatly. Nanomaterials can be used as a drug carrier for several therapeutic agents, which can improve their overall effectiveness through the synergetic action. Moreover, these nanocarriers can be designed to deliver drugs at particular locations and times for a targeted treatment.^[105] For instance, employing nanomaterials in blocking blood vessels feeding tumors (antiangiogenic treatment) can lead to an uneven blood circulation in the tumor and subsequently heighten the chances of cancer returning. Animal studies show that using this approach combined with chemotherapy reduces the rate of tumor recurrence. In a different instance, scientists invented a specific type of nanocarrier for simultaneous delivery of olaparib and JQ1 (a small-molecule prototype of the BET inhibitor) in the management of non-BRCA mutant pancreatic cancer. JQ1 makes cancer cells sensitive to olaparib thereby allowing for the enhancement of treatment—showing that the application of multi-drug nanocarriers improves the effectiveness of the therapy and diminished side effects.^[106] The disease-oriented creation in nanomedicine for personalized cancer care offers various opportunities for the creation of new cancer medications, however, there are still many hurdles to overcome before getting the nod for its application in hospitals. Building these advanced nanomaterials presents an issue, in that it can make the process complicated and expensive. Besides, their mul-

tifunctionality makes it difficult to develop quality control and assessment methods that can be applicable not only in pre-clinical studies but also in hospital use.

To surmount these difficulties, a collaborative effort will be necessary as various branches of science must work together to fulfill the main needs of the industry and the healthcare system, including the processes of safe manufacturing, transportation, and quality assurance. Furthermore, as these nanoparticles apply sophisticated mechanisms of action, the methodologies of testing, as well as the structure of clinical trials, have to be specifically adapted to suit the mechanisms and functions of the drugs.^[107] Modern strategies in cancer nanomedicine rely on patient stratification to determine which patients are more likely to respond positively to treatments, moreover, the discovery of biomarkers that allow for predictions regarding nanocarrier behavior in patients will significantly improve clinical trial planning and the application of new therapies in practice (Fig. 9).^[108] Nanomaterials with intelligence possess significant potential for cancer diagnosis and treatment. The progress made in this area allows for the realization of intricate nanomaterials equipped with high-tech functions and capable of performing challenging multi-step operations based on patient-specific information received from such nanomaterials. The future research should mainly focus on development of methods for analyzing the efficacy of combination therapies, customizing such therapies to meet the needs of particular patient, and on having a better understanding of the principles of work of nanomaterials.^[109] This article shows the most outstanding obstacles and future directions in cancer nanomedicine that will need to be considered in future studies.

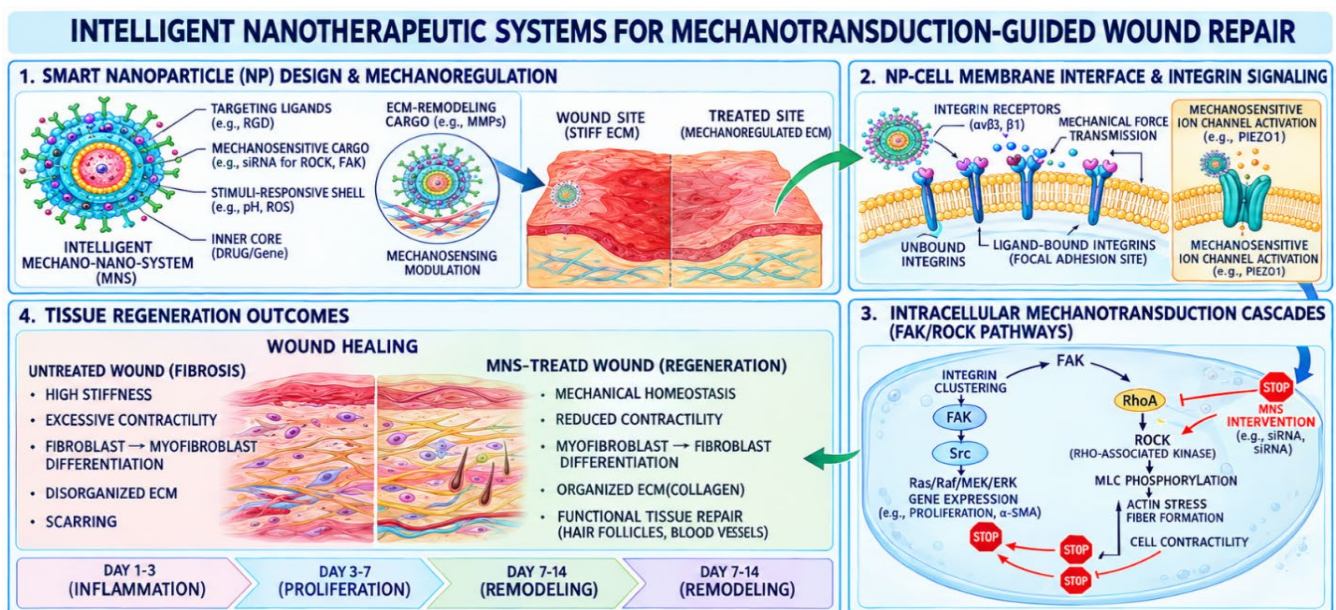


Figure 9. Intelligent nanotherapeutic systems for mechanotransduction-guided wound healing and repair.

Calcium as a Central Rheostat: Unifying Senescence and Wound Healing Dynamics

Cellular senescence has an important role in tumor suppression; however, its frequency rises with age and contributes to cellular dysfunction in diseases such as diabetes and age-related problems. Recent studies show that what used to be considered inactive senescent cells now appear to perform several active biological functions. Transient-cell senescence provides support for normal growth and tissue repair while persistent-cell senescence is found in chronic tissue diseases. From this information, it is possible to identify therapeutic approaches concerning wounds and other skin issues based on senescence mechanisms. The reason for this phenomenon is that aged people cannot recover their body tissues effectively because of an increasing amount of senescent cells.^[64] Recent research shows that cellular senescence may play a role in healthy tissue formation during embryonic development as well as be beneficial for wound healing (Fig. 10). Studies on different organisms have uncovered the previously unknown positive side of cellular senescence. The paper investigates the senescence phenotype in detail, exploring its possible positive and negative aspects in relation to tissue regeneration. The skeletal muscle is critical in a regeneration process, going through the specific and well-established processes in the signaling system. Understanding calcium signaling's role when it comes to muscle development, regeneration, and general homeostasis is of utmost importance. The dynamics of calcium and other regulatory factors are critical for these processes, and their importance lies in maintaining the appropriate muscle functioning.



Figure 10. Intelligent nanotherapeutic systems for mechanotransduction-guided wound healing and tissue repair.

Calcium is very important in the processes of the differentiation of myoblasts and their growth. Calcium signaling occurs during the injury as part of the response of cells to the stressful condition, and this signaling leads to the process of regeneration in muscles through the activation of satellite cells.

However, fully understanding how calcium signaling is related to aging remains a difficult task. Additionally, calcium signaling is necessary for the functioning of epithelial cells, which have important roles in the human organism and carry out lots of functions. This signaling pathway is necessary for regulating such processes as cell growth, movement, differentiation, and death.^[110] Accepting calcium-signaling systems in epithelial tissue development is important. Techniques like computational modeling and quantitative imaging can help reveal these properties.^[9] These discoveries will serve to facilitate progress within the field of regenerative medicine. Several cellular pathways have been utilized in wound healing process, but calcium pathways have been specifically important in cellular senescence and wound healing overall. The scientific literature demonstrates a strong connection between cellular senescence and the diseases linked with increased age, particularly the involvement of calcium signaling in this process. The required alterations in intracellular calcium levels lead to the onset and development of senescence, which is why the cells adjust their movement and metabolism in response to long-lasting (chronic) diseases.^[111] A decrease in mitochondrial Ca^{2+} affects metabolism by changing gene expression related to fibroblast differentiation.^[112] Cellular senescence is crucial for tissue growth, creating inflammatory signals and preventing tumor growth.^[113] As people age with diabetes, senescent cells accumulate in chronic wounds due to various damaging factors. There has been significant interest in clinical trials for drugs that target senescent cells (senolytic drugs and related drugs) for the treatment and prevention of diseases like chronic non-healing wounds. As the aged population continues to rise, a more profound understanding of aging will aid plastic surgeon practices and enhance their care of patients.^[114] Age-related conditions are associated with cellular senescence, which is stable cell cycle stasis, either having a beneficial or negative impact driven by the biology of the situation. This article aims to review the biological role of cell senescence in aging, tissue regeneration, and skin restoration, before discussing new data on the progress and efforts in the field of anti-aging therapies including the modification of senescence (Fig. 11).^[115]

Cellular senescence leads to tumor progression, reduces the immune system's effectiveness, and causes age-related illnesses; paradoxically, it can also protect against cancer. New treatment methods must be focused on this situation. Senolytic medicine, for example, may be aimed at senescent cells only, even though there still need to be clinical trials to check if these treatments are effective and cannot be harmful. The development of senescence detection methods also needs to be enhanced, for instance, the use of urinary exosomes with some markers of senescence can be employed for the determination of renal senescence. Eventually, the

protocol of their collection and analysis needs to be standardized. Biomarkers of future aging might be essential in managing patients. The article explores the interaction of aging cells with metabolic processes that violate organs' normal state and lead to the onset of diseases. In addition, the senescence-associated secretory phenotype (SASP) can trigger the process of aging by establishing both the migration and activity of immune cells in tissues.

Harnessing Neutrophil Functions in Wound Healing and Tissue Regeneration

Neutrophils have been researched extensively for their functions regarding the healing of injuries and diseases, including their ability to regenerate tissues, their influence on how tissues function, and their functions against bacteria. They are among the first cells to be present at infection zones and thus play a considerable role in healing.^[116] The key role of the neutrophils' wide range of antimicrobial agents in minimizing inflammation, eradication of pathogens, clearance from the cellular debris, and in promoting tissue repair is discussed. The important role of the neutrophils in the skin wound healing process is emphasized as it concerns with clearing damaged cells and promoting regeneration of the tissue and the key mechanisms and recent findings related to this immune cell are discussed.^[117] Neutrophils facilitate the healing process

by facilitating angiogenesis (formation of new blood vessels) and cellular proliferation which promote overall health of the tissues. In addition, they play a vital role in eradicating the pathogens with the help of processes like neutrophil extracellular traps (NETs) and proteases, thus affecting the broader dynamics between the immune system and the skin cells when healing is taking place.^[118] The function of signaling molecules in stimulating pro-inflammatory responses together with the development of myofibroblasts during tissue remodeling was studied; neutrophils take part in both pro-inflammatory and anti-inflammatory phases of the process of repairing damaged tissues (Fig. 12). The proper clearance of neutrophils due to apoptosis and reverse transmigration is important, as the improper clearance of neutrophils can interfere with tissue repair and can lead to prolonged inflammation.^[119] In conditions such as diabetic ulcers where normal processes of healing are disrupted, neutrophils can worsen the damage of the tissue. Targeting neutrophils in therapy for inflammation is promising, but the details of their activity, i.e., the spatial and temporal dynamics, are poorly understood. The ability to distinguish triggers of resolution of the inflammatory process from those that lead to chronic inflammatory state is important, as well as understanding the role of neutrophils in both pathways.^[120]

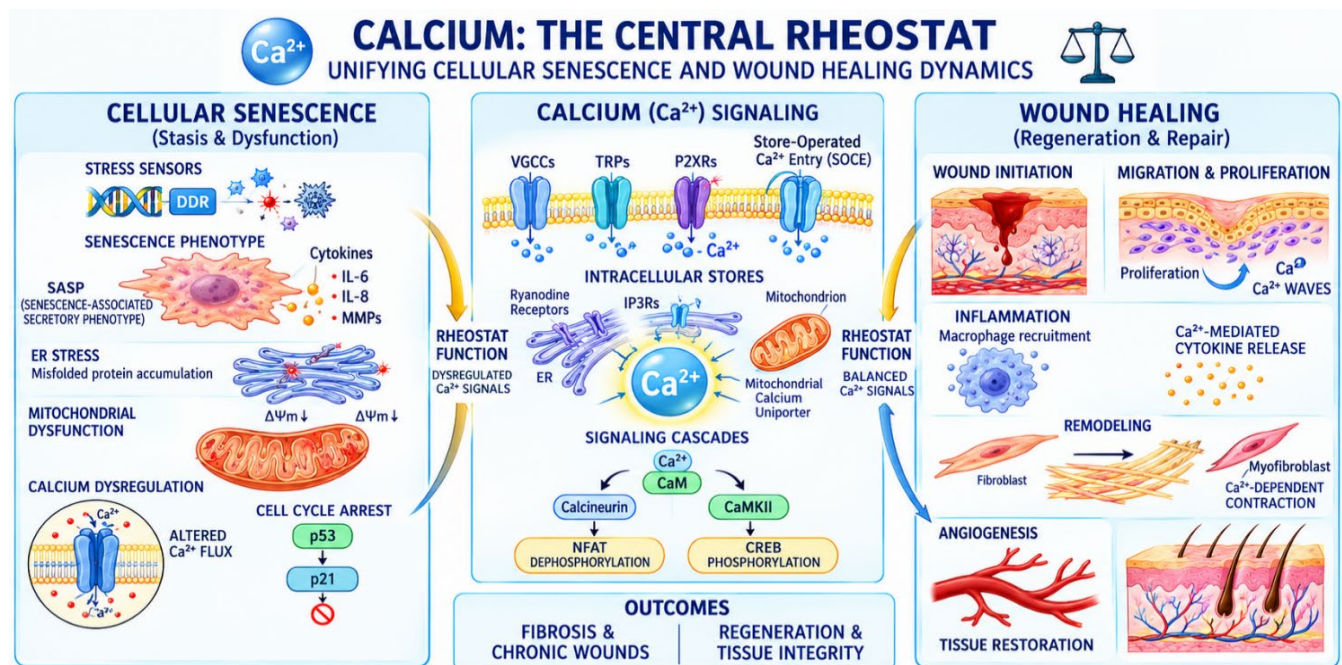


Figure 11. Intelligent nanotherapeutic systems aid in wound healing by responding to mechanical signals. They target and adjust cell processes like migration, inflammation, and tissue repair. These platforms aim to restore proper cellular signaling for better tissue regeneration and repair.

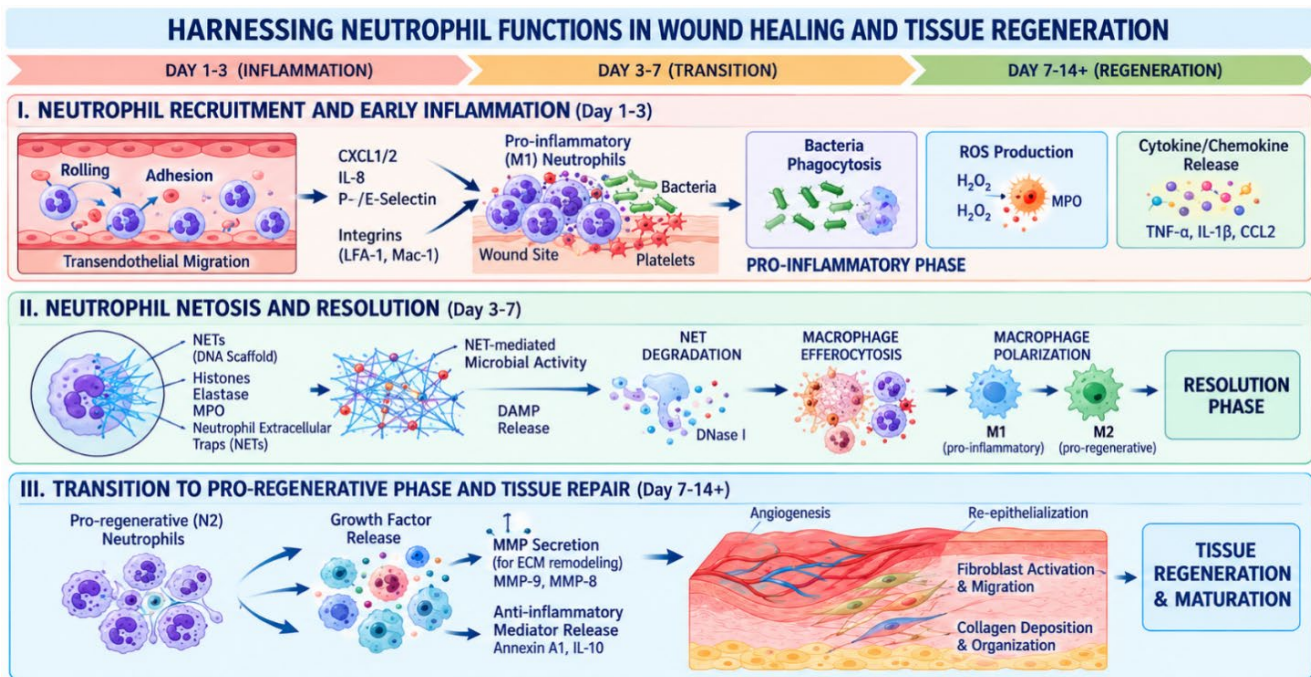


Figure 12. Neutrophil functions in wound healing and tissue regeneration: mechanisms and therapeutic opportunities.

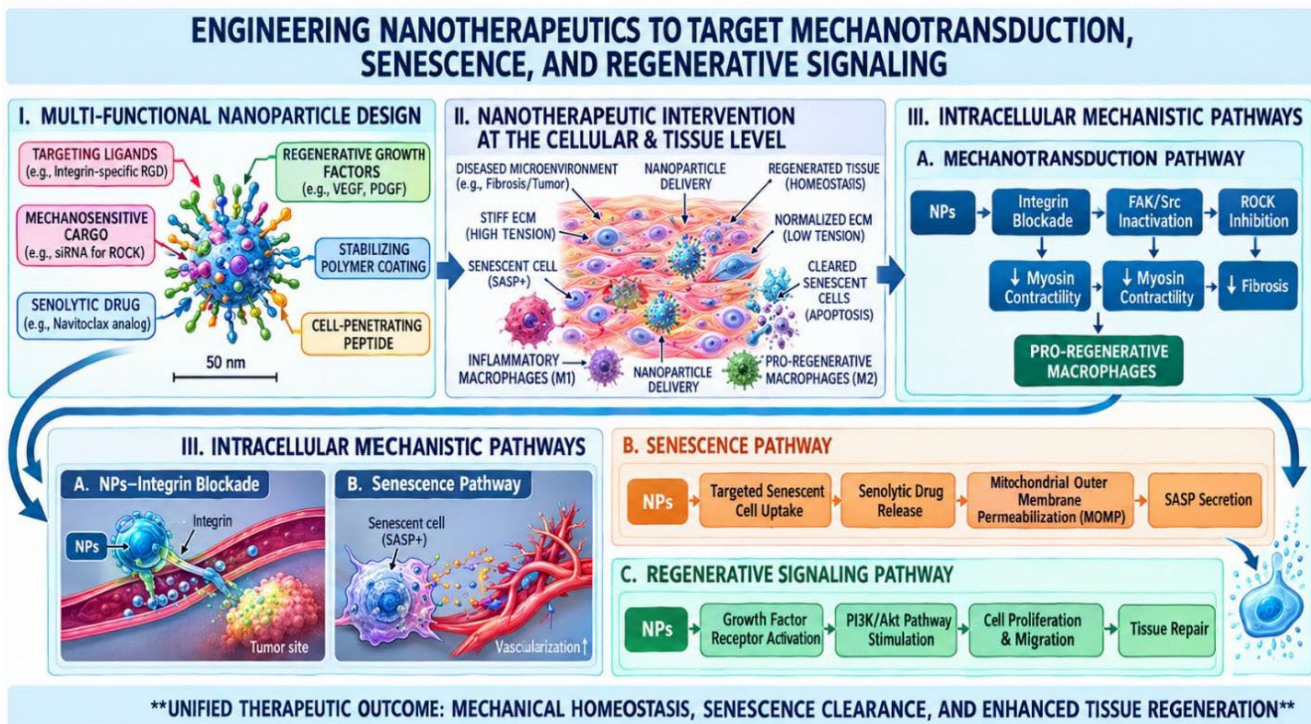


Figure 13. From signals to solutions: integrating mechanotransduction cues into nanotherapeutic design.

In humans, congenital neutrophil disorders have been associated with poor wound healing although current research has relied mostly on animal models. These disorders can have serious repercussions such as pain, loss of function, amputation, and high costs which are frequently caused by abnormal inflammation and excessive formation of neutrophil extracellular traps (NET).^[121] Research on NETs in wound healing examines their role in diabetic and normal wounds and therapies targeting NETs.^[122] NETs can slow wound healing by increasing inflammation and disrupting important processes. Anti-NET treatments may help speed healing.^[116] Research into the signaling systems governing the healing process of damaged tissues seeks to uncover how cellular and molecular processes regulate inflammation and mediate effective healing mechanisms. The healing of a wound consists of three main stages, namely the inflammatory phase, the proliferative phase, and the remodeling phases, making it one of the more complex biological processes.^[123] External molecules like growth factors, cytokines, and chemokines interact with each other within the extracellular matrix and influence various cellular and tissue functions. Studies of the pathways by which signaling occurs show the important role played by important chemical substances in the process of wound healing.^[124] The study found that extracellular stimuli influence intracellular pathways in tissue regeneration.^[125] While the extracellular matrix surrounding the cell is being repaired, the cell itself remains in a homeostatic physiological condition. Modern technological advances have been particularly successful in reproducing biological processes, such as the process of healing and regeneration of tissues.^[53] The focus is on understanding processes that hinder healing and tissue repair in chronic inflammation, highlighting the need for further research for a quick recovery.

Conclusion

The article discusses the way nanotherapeutics can interact with properties involved in mechanosensation, cellular senescence, and regenerative signaling in wound healing. At the same time, the authors consider mechanotransduction to be the process through which mechanical information is perceived by cells and transformed in relevant biochemical responses (that is, through signal transduction pathways information received mechanically can be transformed into biochemical signals). Understanding the essence of mechanisms involved in this process allows the creation of nanotherapeutics, which will be able to work efficiently on the disrupted mechanosensor network leading to effective treatment of chronic and non-healing wounds given the necessity of correcting the functioning of the given network and the information it processes.

This article focuses on the application of nanotherapies to target cellular senescence and control regeneration signaling

pathways. Senescence is generally associated with aging and disease processes; however, it plays also an important physiological role in situations like development and wound healing. As such, this article aims to analyze both the positive and negative role of senescence in tissue regeneration, along with various methods of utilizing its beneficial aspects. Calcium signaling has been identified as a common factor to connect senescence to tissue healing, thus opening doors for new therapeutic modalities. The issue of the immune system as a participant in wound healing process is reviewed from the point of view of the use of immunomodulatory nanotherapies with a specific focus on how the changes in the tissues due to aging and diseases affect the behavior of immune cells, which could be helpful in treatment of diseases like cancer or fibrosis. The burgeoning field of mechanobiology, which underscores the influence of mechanobiology on immune system's functioning, has also been reviewed (Fig. 13). The article also broaches the subject of neutrophil functioning in the context of healing and regeneration of tissues. The researchers also highlight innovative systems based on the principles of nanotechnology, which could regulate wound healing via mechanoresponsive systems. There are also some expectations concerning the realization of such novel techniques for tackling chronic wounds and other types of similar ailments. The article also encompasses the role of pharmacological agents, which could achieve the reduction of inflammation and promote healing according to the results obtained via diverse experimental techniques.

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Author contributions

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Declaration of Competing Interest

The authors declare that they have no known competing fi-

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Data availability statement

Given the nature of the research, [ethical, legal or commercial] supporting data is irrelevant and therefore not provided.

References and notes

- [1] Zhao M, Wang L, Wang M, Zhou S, Lu Y, Cui H, et al. Targeting fibrosis, mechanisms and clinical trials. Vol. 7, Signal Transduction and Targeted Therapy. 2022.
- [2] Varadan VK. The role of nanotechnology and nano and micro-electronics in monitoring and control of cardiovascular diseases and neurological disorders. In: Nanosensors, Microsensors, and Biosensors and Systems 2007. 2007.
- [3] El-Fiqi A, Mandakhbayar N, Jo S Bin, Knowles JC, Lee JH, Kim HW. Nanotherapeutics for regeneration of degenerated tissue infected by bacteria through the multiple delivery of bio-active ions and growth factor with antibacterial/angiogenic and osteogenic/odontogenic capacity. *Bioact Mater*. 2021; 6(1): 123–36.
- [4] Mendes PM. Cellular nanotechnology: Making biological interfaces smarter. *Chemical Society Reviews*. 2013.
- [5] Said A, Naeem N, Siraj S, Khan T, Javed A, Rasheed HM, et al. Mechanisms underlying the wound healing and tissue regeneration properties of *Chenopodium album*. *3 Biotech*. 2020;
- [6] Kumar R. Emerging Role of Neutrophils in Wound Healing and Tissue Repair: The Routes of Healing. *Biomed J Sci Tech Res*. 2021; 36(4): 28687–8.
- [7] Wang N, Lu Y, Rothrauff BB, Zheng A, Lamb A, Yan Y, et al. Mechanotransduction pathways in articular chondrocytes and the emerging role of estrogen receptor- α . Vol. 11, *Bone Research*. 2023.
- [8] McLaughlin S, Podrebarac J, Ruel M, Suuronen EJ, McNeill B, Alarcon EI. Nano-engineered biomaterials for tissue regeneration: What has been achieved so far? Vol. 3, *Frontiers in Materials*. Frontiers Media S.A.; 2016.
- [9] Leanza L, Biasutto L, Managò A, Gulbins E, Zoratti M, Szabò I. Intracellular ion channels and cancer. Vol. 4 SEP, *Frontiers in Physiology*. 2013.
- [10] Rajiv K. Mechanosensors, and Mechanosensing: Mechanosensation, a Perception of the Force and Response. *Glob J Med Res C Microbiol Pathol*. 2021; 21(2): 1–3.
- [11] Robertson SN, Campsie P, Childs PG, Madsen F, Donnelly H, Henriquez FL, et al. Control of cell behaviour through nanovibrational stimulation: Nanokicking. Vol. 376, *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*. Royal Society Publishing; 2018.
- [12] Doyle AD, Yamada KM. Mechanosensing via cell-matrix adhesions in 3D microenvironments. *Experimental Cell Research*. 2016.
- [13] Huang S, Ingber DE. Cell tension, matrix mechanics, and cancer development. Vol. 8, *Cancer Cell*. 2005.
- [14] Ohashi K, Fujiwara S, Mizuno K. Roles of the cytoskeleton, cell adhesion and rho signalling in mechanosensing and mechanotransduction. Vol. 161, *Journal of Biochemistry*. 2017.
- [15] Plant AL, Bhadriraju K, Spurlin TA, Elliott JT. Cell response to matrix mechanics: Focus on collagen. Vol. 1793, *Biochimica et Biophysica Acta - Molecular Cell Research*. 2009.
- [16] Hansel CS, Crowder SW, Cooper S, Gopal S, Joao Pardelha Da Cruz M, De Oliveira Martins L, et al. Nanoneedle-Mediated Stimulation of Cell Mechanotransduction Machinery. *ACS Nano*. 2019;
- [17] Wolfenson H, Yang B, Sheetz MP. Steps in Mechanotransduction Pathways that Control Cell Morphology. *Annu Rev Physiol*. 2019;
- [18] Varadarajan S, Stephenson RE, Miller AL. Multiscale dynamics of tight junction remodeling. *Journal of Cell Science*. 2019.
- [19] Santos MI, Tuzlakoglu K, Fuchs S, Gomes ME, Peters K, Unger RE, et al. Endothelial cell colonization and angiogenic potential of combined nano- and micro-fibrous scaffolds for bone tissue engineering. *Biomaterials*. 2008;
- [20] Rajiv K. Cell Shrinkage, Cytoskeletal Pathologies, and Neurodegeneration: Myelin Sheath Formation and Remodeling. *Arch Med Clin Res*. 2021; 1(1): 1–5.
- [21] Rajiv Kumar and Mitrabasu Chhillar. Nano-bio interface, bioadaptability of different nanoparticles, nanokicking and extracellular matrix mimicking: a biological and medicinal front to promote the concept of a cell, having a better defense system inbuilt by nature. *Aditum J Clin Biomed Res*. 2021; 1(5): 1–7.
- [22] Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. *World Allergy Organization Journal*. 2012.
- [23] Korkina LG, Mikhail'chik E V., Suprun M V., Pastore S, Dal Toso R. Molecular mechanisms underlying wound healing and anti-inflammatory properties of naturally occurring biotechnologically produced phenylpropanoid glycosides. *Cell Mol Biol*. 2007;
- [24] Geng X, Liu B, Liu J, Liu D, Lu Y, Sun X, et al. Interfacial tissue engineering of heart regenerative medicine based on soft cell-porous scaffolds. *Journal of Thoracic Disease*. 2018.
- [25] Dong Y, Chen H, Gao J, Liu Y, Li J, Wang J. Molecular machinery and interplay of apoptosis and autophagy in coronary heart disease. Vol. 136, *Journal of Molecular and Cellular Cardiology*. Academic Press; 2019. p. 27–41.
- [26] Hoang DM, Pham PT, Bach TQ, Ngo ATL, Nguyen QT, Phan TTK et al. Stem cell-based therapy for human diseases. *Signal Transduct Target Ther*. 2022; 7(1): 272.
- [27] Jo J, Abdi Nansa S, Kim DH. Molecular Regulators of Cellular Mechanoadaptation at Cell–Material Interfaces. Vol. 8, *Frontiers in Bioengineering and Biotechnology*. Frontiers Media S.A.; 2020.
- [28] Kumar R, Gulia K. The convergence of nanotechnology - stem cell, nanotopography - mechanobiology, and biotic - abiotic

- interfaces: Nanoscale tools for tackling the top killer, arteriosclerosis, strokes, and heart attacks. *Nano Sel.* 2021; 2(4): 655–87.
- [29] Zhang X, Zhang S, Wang T. How the mechanical microenvironment of stem cell growth affects their differentiation: a review. Vol. 13, *Stem Cell Research and Therapy*. 2022.
- [30] Elks PM, Renshaw SA, Meijer AH, Walmsley SR, Van Eeden FJ. Exploring the HIFs, butts and maybes of hypoxia signalling in disease: Lessons from zebrafish models. *DMM Disease Models and Mechanisms*. 2015.
- [31] Verma S, Domb AJ, Kumar N. *Nanomaterials for regenerative medicine*. Vol. 6, *Nanomedicine*. 2011.
- [32] Liu J, Radja A, Gao Y, Yin R, Sweeney A, Yang S. Mimicry of a biophysical pathway leads to diverse pollen-like surface patterns. *Proc Natl Acad Sci U S A*. 2020; 117(18): 9699–705.
- [33] Llopis-Hernández V, Rico P, Ballester-Beltrán J, Moratal D, Salmerón-Sánchez M. Role of surface chemistry in protein remodeling at the cell-material interface. *PLoS One*. 2011; 6(5).
- [34] Gao J, Liao C, Liu S, Xia T, Jiang G. *Nanotechnology: new opportunities for the development of patch - clamps*. Vol. 19, *Journal of Nanobiotechnology*. 2021.
- [35] Reshetilov AN, Bezborodov AM. *Nanobiotechnology and biosensor research*. Vol. 44, *Prikladnaia biokhimiia i mikrobiologiya*. 2008.
- [36] Gulia RK and K. Cell Mechanotransduction Machinery, and Cell Signaling Defects: Small Tools and Nano-Bio Interface for Influential Regenerative Remedies. *J Cell Signal*. 2021; 6(5): 1–14.
- [37] Kumar R, Chhillar N. Mimicry at the Material-Cell Interface. In: *Biomimicry Materials and Applications*. 2023.
- [38] Ladoux B, Nelson WJ, Yan J, Mège RM. The mechanotransduction machinery at work at adherens junctions. *Integrative Biology (United Kingdom)*. 2015.
- [39] Rajiv K. Biomedical applications of nanoscale tools and nano-bio interface: A blueprint of physical, chemical, and biochemical cues of cell mechanotransduction machinery. *Biomed Res Clin Rev*. 2021; 4(2): 64, 1-4.
- [40] Seshadri DR, Ramamurthi A. Nanotherapeutics to modulate the compromised micro-environment for lung cancers and chronic obstructive pulmonary disease. Vol. 9, *Frontiers in Pharmacology*. 2018.
- [41] Kamila S, McEwan C, Costley D, Atchison J, Sheng Y, Hamilton GRC, et al. Diagnostic and therapeutic applications of quantum dots in nanomedicine. In: *Topics in Current Chemistry*. 2016.
- [42] Lovett ML, Nieland TJF, Dingle YTL, Kaplan DL. Innovations in 3D Tissue Models of Human Brain Physiology and Diseases. Vol. 30, *Advanced Functional Materials*. 2020.
- [43] Brunetti V, Maiorano G, Rizzello L, Sorce B, Sabella S, Cingolani R, et al. Neurons sense nanoscale roughness with nanometer sensitivity. *Proc Natl Acad Sci U S A*. 2010;
- [44] Yadid M, Feiner R, Dvir T. Gold Nanoparticle-Integrated Scaffolds for Tissue Engineering and Regenerative Medicine. *Nano Lett*. 2019;
- [45] Sonali, Viswanadh MK, Singh RP, Agrawal P, Mehata AK, Pawde DM, et al. *Nanotheranostics: Emerging strategies for early diagnosis and therapy of brain cancer*. Vol. 2, *Nanotheranostics*. 2018.
- [46] Kumar R, Chhikara BS, Zeybekler SE, Gupta DS, Kaur G, Chhillar M, et al. Nanotoxicity of multifunctional stoichiometric cobalt oxide nanoparticles (SCoONPs) with repercussions toward apoptosis, necrosis, and cancer necrosis factor (TNF- α) at nano-biointerfaces. Vol. 12, *Toxicology Research*. 2023.
- [47] M. F-B. *Nanotechnology in diagnostic and pharmacotherapy - Future medicine*. *Folia Neuropathologica*. 2011.
- [48] Oudinet C, Braikia FZ, Dauba A, Khamlichi AA. Recombination may occur in the absence of transcription in the immunoglobulin heavy chain recombination centre. *Nucleic Acids Res*. 2020; 48(7): 3553–66.
- [49] Stoll H, Kwon IK, Lim JY. Material and mechanical factors: New strategy in cellular neurogenesis. *Neural Regeneration Research*. 2014.
- [50] Tsukioka T, Hiratsuka T, Nakamura M, Watanabe T, Kitamura Y, Isobe K, et al. An on-site preparable, novel bone-grafting complex consisting of human platelet-rich fibrin and porous particles made of a recombinant collagen-like protein. *J Biomed Mater Res - Part B Appl Biomater*. 2019;
- [51] Gingold J, Zhou R, Lemischka IR, Lee DF. Modeling Cancer with Pluripotent Stem Cells. Vol. 2, *Trends in Cancer*. 2016.
- [52] Kumar N, Kumar R. *Nanotechnology and Nanomaterials in the Treatment of Life-Threatening Diseases*. *Nanotechnology and Nanomaterials in the Treatment of Life-Threatening Diseases*. 2013.
- [53] Rajiv Kumar, Sandeep Mittan JS. Nanobiomaterials, nanobiomechanics and tissue bioengineering for advanced regenerative therapeutics: present and future perspectives. *J Mater Nanosci*. 2015; 2(1): 15–26.
- [54] Kumar R, Chhillar N, Gupta DS, Kaur G, Singhal S, Chauhan T. Cholesterol Homeostasis, Mechanisms of Molecular Pathways, and Cardiac Health: A Current Outlook. Vol. 49, *Current Problems in Cardiology*. 2024.
- [55] Chen CS. Mechanotransduction - A field pulling together? *J Cell Sci*. 2008;
- [56] Van Rijt S, Habibovic P. Enhancing regenerative approaches with nanoparticles. *Journal of the Royal Society Interface*. 2017.
- [57] Hu M, Ling Z, Ren X. Extracellular matrix dynamics: tracking in biological systems and their implications. Vol. 16, *Journal of Biological Engineering*. 2022.
- [58] Qamar SA, Asgher M, Khalid N, Sadaf M. *Nanobiotechnology in health sciences: Current applications and future perspectives*. Vol. 22, *Biocatalysis and Agricultural Biotechnology*. 2019.
- [59] Kolimi P, Narala S, Nyavanandi D, Youssef AAA, Dudhipala N.

- Innovative Treatment Strategies to Accelerate Wound Healing: Trajectory and Recent Advancements. Vol. 11, Cells. 2022.
- [60] Elder DE. Melanoma progression. Pathology. 2016; 48(2): 147–54.
- [61] Vernengo AJ, Grad S, Eglin D, Alini M, Li Z. Bioprinting Tissue Analogues with Decellularized Extracellular Matrix Bioink for Regeneration and Tissue Models of Cartilage and Intervertebral Discs. Adv Funct Mater. 2020; 30(44).
- [62] NCT01270139. Plasmonic Nanophotothermal Therapy of Atherosclerosis. <https://clinicaltrials.gov/show/NCT01270139>. 2011;
- [63] Herranz N, Gil J. Mechanisms and functions of cellular senescence. Vol. 128, Journal of Clinical Investigation. 2018.
- [64] Wiley CD, Campisi J. The metabolic roots of senescence: mechanisms and opportunities for intervention. Vol. 3, Nature Metabolism. 2021.
- [65] Kalyanaraman B, Cheng G, Hardy M, Ouari O, Bennett B, Zielonka J. Teaching the basics of reactive oxygen species and their relevance to cancer biology: Mitochondrial reactive oxygen species detection, redox signaling, and targeted therapies. Redox Biology. 2018.
- [66] Asano S, Ito S, Morosawa M, Furuya K, Naruse K, Sokabe M, et al. Cyclic stretch enhances reorientation and differentiation of 3-D culture model of human airway smooth muscle. Biochem Biophys Reports. 2018; 16.
- [67] Hieda M. Signal transduction across the nuclear envelope: Role of the LINC complex in bidirectional signaling. Vol. 8, Cells. 2019.
- [68] Wang L, Nakamura F. Identification of Filamin A Mechanobinding Partner I: Smoothelin Specifically Interacts with the Filamin A Mechanosensitive Domain 21. Biochemistry. 2019; 58(47).
- [69] Thomasy SM, Morgan JT, Wood JA, Murphy CJ, Russell P. Substratum stiffness and latrunculin B modulate the gene expression of the mechanotransducers YAP and TAZ in human trabecular meshwork cells. Exp Eye Res. 2013; 113.
- [70] Huang Q, Lee J, Arce FT, Yoon I, Angsantikul P, Liu J, et al. Nanofibre optic force transducers with sub-piconewton resolution via near-field plasmon-dielectric interactions. Nat Photonics. 2017; 11(6).
- [71] Zhao D, Liu S, Gao Y. Single-molecule manipulation and detection. Vol. 50, Acta Biochimica et Biophysica Sinica. 2018.
- [72] Cordova JC, Das DK, Manning HW, Lang MJ. Combining single-molecule manipulation and single-molecule detection. Vol. 28, Current Opinion in Structural Biology. 2014.
- [73] Fisher TE, Marszalek PE, Fernandez JM. Stretching single molecules into novel conformations using the atomic force microscope. Vol. 7, Nature Structural Biology. 2000.
- [74] Yadav D, Garg RK, Chhabra D, Yadav R, Kumar A, Shukla P. Smart diagnostics devices through artificial intelligence and mechanobiological approaches. Vol. 10, 3 Biotech. 2020.
- [75] Hwang PY, Mistriotis P, Cai H, Liu L, Zhang B, Smith Q, et al. Frontiers in mechanobiology and mechanomedicine. Med-X. 2025; 3(1): 23.
- [76] Lin X, Yang H, Xia Y, Wu K, Chu F, Zhou H, et al. Mechanobiomaterials: Harnessing mechanobiology principles for tissue repair and regeneration. Vol. 2, Mechanobiology in Medicine. 2024.
- [77] Wang W, Lu KJ, Yu CH, Huang QL, Du YZ. Nano-drug delivery systems in wound treatment and skin regeneration. Journal of Nanobiotechnology. 2019.
- [78] Nandhini J, Karthikeyan E, Rajeshkumar S. Nanomaterials for wound healing: Current status and futuristic frontier. Vol. 6, Biomedical Technology. 2024.
- [79] Bramhill J, Ross S, Ross G. Bioactive nanocomposites for tissue repair and regeneration: A review. Vol. 14, International Journal of Environmental Research and Public Health. 2017.
- [80] Smith LA, Liu X, Ma PX. Tissue engineering with nano-fibrous scaffolds. Soft Matter. 2008; 4(11).
- [81] Lim CG, Jang J, Kim C. Cellular machinery for sensing mechanical force. Vol. 51, BMB Reports. 2018.
- [82] Saffioti NA, Cavalcanti-Adam EA, Pallarola D. Biosensors for Studies on Adhesion-Mediated Cellular Responses to Their Microenvironment. Vol. 8, Frontiers in Bioengineering and Biotechnology. 2020.
- [83] Chatterjee S. Endothelial mechanotransduction, redox signaling and the regulation of vascular inflammatory pathways. Vol. 9, Frontiers in Physiology. Frontiers Media S.A.; 2018.
- [84] Abdollahiyan P, Oroojalian F, Mokhtarzadeh A. The triad of nanotechnology, cell signalling, and scaffold implantation for the successful repair of damaged organs: An overview on soft-tissue engineering. Vol. 332, Journal of Controlled Release. 2021.
- [85] Moniri Javadhesari S, Koohi M, Jabraili M. Nanomaterials: Applications in Regeneration of Damaged Tissues. Adv Ceram Prog. 2022; 8(4).
- [86] Sutanto H, Lyon A, Lumens J, Schotten U, Dobrev D, Heijman J. Cardiomyocyte calcium handling in health and disease: Insights from in vitro and in silico studies. Prog Biophys Mol Biol. 2020; 157.
- [87] Wilkinson HN, Hardman MJ. Senescence in Wound Repair: Emerging Strategies to Target Chronic Healing Wounds. Vol. 8, Frontiers in Cell and Developmental Biology. 2020.
- [88] Gao M, Guo H, Dong X, Wang Z, Yang Z, Shang Q, et al. Regulation of inflammation during wound healing: the function of mesenchymal stem cells and strategies for therapeutic enhancement. Vol. 15, Frontiers in Pharmacology. 2024.
- [89] Chen F, Wu P, Zhang H, Sun G. Signaling Pathways Triggering Therapeutic Hydrogels in Promoting Chronic Wound Healing. Vol. 24, Macromolecular Bioscience. 2024.
- [90] Bonnici L, Suleiman S, Schembri-Wismayer P, Cassar A. Targeting Signalling Pathways in Chronic Wound Healing. Vol. 25, International Journal of Molecular Sciences. 2024.
- [91] Rat A, Martinez Fernandez V, Doumic M, Teixeira MT, Xu Z. Mathematical model linking telomeres to senescence in Sac-

- charomyces cerevisiae reveals cell lineage versus population dynamics. *Nat Commun*. 2025; 16(1).
- [92] Liang C, Liu Z, Song M, Li W, Wu Z, Wang Z, et al. Stabilization of heterochromatin by CLOCK promotes stem cell rejuvenation and cartilage regeneration. *Cell Res*. 2021; 31(2).
- [93] Qu X, Wu P, Duan K, Wang G, Gao LL, Guo Y, et al. Self-calibrating probes constructed on a unique dual-emissive fluorescence platform for the precise tracking of cellular senescence. *Chinese Chem Lett*. 2024; 35(12).
- [94] Wallis R, Mizen H, Bishop CL. The bright and dark side of extracellular vesicles in the senescence-associated secretory phenotype. *Mech Ageing Dev*. 2020; 189.
- [95] Labbadia J, Morimoto RI. The biology of proteostasis in aging and disease. Vol. 84, *Annual Review of Biochemistry*. 2015.
- [96] Li K, Jin J, Yang Y, Luo X, Wang Y, Xu A, et al. Application of Nanoparticles for Immunotherapy of Allergic Rhinitis. Vol. 19, *International Journal of Nanomedicine*. 2024.
- [97] Wei X, Guan P, Fang J, Yin J, Xu Z, Li C, et al. Kaempferol-ZIF-8 Hybrid System Augments Bioadhesive Thermoresponsive Hydrogel for Enhanced Diabetic Wound Healing. *Adv Healthc Mater*. 2026; 15(25).
- [98] Chalk F, Palmer A. The impact of ageing and frailty on wound healing. *Br J Nurs*. 2025; 34(20).
- [99] Zhao L, Gao Z, Yuan Z, Yang X, Li D, Ren Q, et al. DC-CD4 bispecific tolerogenic nanovesicles induce antigen-specific regulatory T cells and ameliorate collagen-induced arthritis in mice. *Nat Commun*. 2026; 17(1): 4170.
- [100] Kiyono H, Ernst PB. Nasal vaccines for respiratory infections. Vol. 641, *Nature*. 2025.
- [101] Ru Y, Cai Y, Cheng G, Ma X, Jiang J, Song J, et al. Immune cells in diabetic wound repair: the key to better wound management. *Frontiers of Medicine*. 2025.
- [102] Soheilifar MH, Masoudi-Khoram N, Hassani M, Hajialiasgari Najafabadi A, Khojasteh M, Keshmiri Neghab H, et al. Angio-microRNAs in diabetic foot ulcer-: Mechanistic insights and clinical perspectives. Vol. 192, *Progress in Biophysics and Molecular Biology*. 2024.
- [103] Lee J-R. Recent Advances in Polymer-Based Immunomodulatory Nanomaterials for Wound Healing. *Polymers (Basel)*. 2026; 18(11).
- [104] Sousa AB, Águas AP, Barbosa MA, Barbosa JN. Immunomodulatory biomaterial-based wound dressings advance the healing of chronic wounds via regulating macrophage behavior. Vol. 9, *Regenerative Biomaterials*. 2022.
- [105] Wang Y, Du C, Zhao Y, Nie G, Yang Y. Trap and kill strategy for non-BRCA mutant pancreatic cancer by co-delivery of olaparib and JQ1 with plectin-1 targeting peptide nanoparticles. *Nano Today*. 2020; 33.
- [106] Li S, Zhang Y, Ho SH, Li B, Wang M, Deng X, et al. Combination of tumour-infarction therapy and chemotherapy via the co-delivery of doxorubicin and thrombin encapsulated in tumour-targeted nanoparticles. *Nat Biomed Eng*. 2020; 4(7).
- [107] Jones DE, Ghandehari H, Facelli JC. A review of the applications of data mining and machine learning for the prediction of biomedical properties of nanoparticles. Vol. 132, *Computer Methods and Programs in Biomedicine*. 2016.
- [108] Kwon S, Youtie J, Porter A, Newman N. How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. *J Technol Transf*. 2024; 49(1).
- [109] Karati D, Mukherjee S, Dutta A, Ash D, Ganguly SC, Acharya A, et al. Smart Multifunctional Nanoparticles in Cancer Theranostics: Progress and Prospect. *Pharm Nanotechnol*. 2024; 13(4).
- [110] Breckel CA, Hochstrasser M. Ubiquitin ligase redundancy and nuclear-cytoplasmic localization in yeast protein quality control. Vol. 11, *Biomolecules*. MDPI; 2021.
- [111] Guha R, Bender A. Computational Approaches in Cheminformatics and Bioinformatics. *Computational Approaches in Cheminformatics and Bioinformatics*. 2011.
- [112] Kumar R. Wound Pathophysiology: Insights of Ca²⁺ Signaling and Cellular Senescence Mechanisms in Healing, and Regeneration. *J Blood Disord Transfus*. 2021; 12(4): 1–4.
- [113] Li C, Qiu S, Liu X, Guo F, Zhai J, Li Z, et al. Extracellular matrix-derived mechanical force governs breast cancer cell stemness and quiescence transition through integrin-DDR signaling. *Signal Transduct Target Ther*. 2023; 8(1).
- [114] Multiscale Modeling in Biomechanics and Mechanobiology. *Multiscale Modeling in Biomechanics and Mechanobiology*. Springer London; 2015.
- [115] Elmore S. Apoptosis: A Review of Programmed Cell Death. Vol. 35, *Toxicologic Pathology*. 2007.
- [116] Martinod K, Deppermann C. Immunothrombosis and thromboinflammation in host defense and disease. Vol. 32, *Platelets*. 2021.
- [117] Kaminska B, Gozdz A, Zawadzka M, Ellert-Miklaszewska A, Lipko M. MAPK signal transduction underlying brain inflammation and gliosis as therapeutic target. In: *Anatomical Record*. 2009.
- [118] Rajiv K. Physiology, Coagulation Cascade: Inherited Disorders, and the Molecular Phenomenon of Alterations in Hemostasis. *J Clin Haematol*. 2021; 2(2): 62–4.
- [119] Alzate-Correa D, Lawrence WR, Salazar-Puerta A, Higuera-Castro N, Gallego-Perez D. Nanotechnology-Driven Cell-Based Therapies in Regenerative Medicine. Vol. 24, *AAPS Journal*. 2022.
- [120] Malik S, Muhammad K, Waheed Y. Emerging Applications of Nanotechnology in Healthcare and Medicine. Vol. 28, *Molecules*. 2023.
- [121] Ursini F, Russo E, Pellino G, D'Angelo S, Chiaravalloti A, De Sarro G, et al. Metformin and autoimmunity: A "new deal" of an old drug. Vol. 9, *Frontiers in Immunology*. Frontiers Media S.A.; 2018.
- [122] Zhu S, Yu Y, Ren Y, Xu L, Wang H, Ling X, et al. The emerging roles of neutrophil extracellular traps in wound healing. Vol. 12,

Cell Death and Disease. 2021.

- [123] Rajiv K. Elucidation of the origin of autoimmune diseases via computational multiscale mechanobiology and extracellular matrix remodeling: theories and phenomenon of immunodominance. *Curr Med Drug Res.* 2021; 5(1): Art. ID 215 (2021).
- [124] Irez T, Bicer S, Sahin E, Dutta S, Sengupta P. Cytokines and adipokines in the regulation of spermatogenesis and semen quality. *Chem Biol Lett.* 2020; 7(2): 131–9.
- [125] Momtazi-Borojeni AA, Abdollahi E, Nikfar B, Chaichian S, Ekhlasi-Hundrieser M. Curcumin as a potential modulator of M1 and M2 macrophages: new insights in atherosclerosis therapy. Vol. 24, *Heart Failure Reviews.* Springer; 2019. p. 399–409.