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Review Article

Cell Mechanotransduction Machinery, and Cell Signaling Defects: Small Tools and Nano-Bio Interface for Influential Regenerative Remedies

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ABSTRACT

Designing nanotools and devices offers a wider platform having high therapeutic claims for the discovery of drug discovery and promoting cellular events including cell motility, signaling pathways, cellular proliferation, cell physiology, apoptosis, and microenvironmental conditions during tissue engineering and regeneration. To enhance cellular environment in a physical and chemical context, the nanotools having remedies to care for the endothelial matrix during various cellular processes and mechanisms (nutrient transport, cell health, cellular interactions, differentiation, and proliferation). The influential regenerative remedies were also transported by drug delivery tools and devices for enhancing biophysical interactions with multiple mechanoresponsive that further support healing. Therefore, the small tools and nano-bio interface were also applied for stimulation and rejuvenation. The role of the Wnt/β-Catenin pathway, growth factor-β (TGF-β) signaling, inflammasome, IL-1β, cytokine, cadherin, and Ca2+dependent cell-cell adhesion proteins in the regeneration were underlined and highlighted. The elucidation of interlinked signaling pathways of cellular events offers a new approach for developing novel therapeutic remedies and emerged as new concepts in tissue regeneration and repair. Cell damage tempted injury leads to apoptosis, autophagy, and necroptosis via different processes.

Keywords: Cell mechanotransduction machinery; Intracellular signaling pathways; Nano-Bio tools; Future regenerative therapies

INTRODUCTION

Multifunctional nanomaterials have unique properties in various forms and that could be used in the medical field and devices i.e. in the design of nanocarriers (effective drug delivery of biomolecules) in the formation of the theranostics (in vivo cell tracking and imaging), in the construction of nano-bio tools (therapeutic) for enhancing stem cell fate, and in tissue engineering for nourishing scaffolds. These nanomaterials, nanotechnology, and fabrication methodologies are the best sources to be recommended in the formation and formulation of regenerative remedies [1]. The nano-bio tools have special features and so they can perform at the nanoscale and promote cellular events and tissues as well as these tools can identify existed defects in the functioning styles and activities (cellular adhesion, migration, and differentiation) of cells and tissues. These small tools have been prescribed for healing bone, muscle, cardiovascular, and neural tissue diseases for many years. These small tools and devices can provide a better set of surface molecules required for natural interconnectivity in cellular networks necessary for promoting cell adhesion and proliferation. These findings will re-model the aspects of routes of mechanisms and actions associated with regenerative therapeutic. Some of the developed scaffolds at the nanoscale have three-dimensional architectures and are well equipped with special features required to mimic the extracellular matrix. [2]. Therefore, such biocompatible and nontoxic nanocomposites are in demand in the current trends and prospects, including cell and tissue regeneration. Few of the nanomaterials and nanobiomaterials are highly capable of initiating and boosting the regenerative routes. Therefore, these materials and nanotools reestablish and recover the normal functioning of cells and tissues as was earlier reported [3]. The first goal of regeneration therapy is the healing of injured, wounded, and damaged cells, tissue, or organ, if it cannot recover them, it cannot be regenerated. It is a quite challenging task to heal several chronic injuries and wounds, but now there is hope to cure a few of them with the help of the aforementioned small tools and technology. Soon, the regeneration of the liver, heart, skin, and kidney are outlined and will be a reality. To accomplish these aims, few techniques i.e. nanofabrication, nano-bio technologies, microfluidic systems and, extracorporeal devices will be very helpful. Therefore, the nanodevices and tools are considered as the best option, and are considered as a source for interrelated management strategies applied for healing wounds and further considered as a reliable component in the innovation of novel regenerative medicines. After the innovation of nanotechnology, now it looks quite feasible that the targeted and underlined medical claims can be successfully achieved. Nanotherapeutics are capable of repairing and regenerating the injured, damaged parts or diseased (cells, tissues, organs) to restore the normal functioning them [4]. The emergence of nanotechnology is filling the persisted gaps and complete the much-awaited needs which are highlighted necessarily in the innovation of nanoscale devices [5]. Discussed

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small tools are highly capable and competent to enhance the speed of regeneration and rate of recreation of cells and tissues [6]. These developed regenerative therapeutics showed potential as the best remedies that can heal many incurable injuries and wounds by ruling out the current therapy. The untouched and undisclosed aspects of these strategies are one of their best ability that can heal damages without altering the upstream signaling milieu of cellular processes [7]. The cellular machinery with damaged or ruptured tissues and organs in any incident, or during any pathogenic attack, cannot perform properly and that is why the healing process of these injuries and wounds should be initiated as soon as possible to maintain the proper functioning of the cell [8]. Such interlink between different mechanisms may affect the generation process of cellular signaling, therefore, the alterations occurring in the cell functioning must be analyzed with deep concern [9]. The essence is lying in the extracellular matrix, which consists of nanoscale components and architectures, which can prevent any infections, injuries, diseases, and wounds that can be existed in these nanoscale compartments. To achieve these types of medical objectives, the best option is regenerative remedies. Here, the author underlined the most complicated phenomenon, which has undiscovered features of the blueprint of mechanotransduction mechanisms, happened in different stages. Applied and cell-generated forces change cellular functioning via these common mechanotransduction pathways for maintaining equilibrium. To determine and look into the feasibility of these elements and themes, the recent developments of the concerned field were referred to and discussed in the review. The advanced design of nanoscale tools was recommended for replacing damaged cells, tissues, and organs that will play a significant role in regeneration as nanotherapeutic, and the same was also included in the discussion.

EXTRACELLULAR MATRIX, AND SIGNALING PATHWAYS: CELLULAR MECHANOTRANSDUCTION

The cell-cell and cell-extracellular matrix interactions occur in the cellular compartments and if these events and activities are interrupted by any means, then these hindrances are further overly involved in creating perturbations in the cell functioning [10]. In the literature, a multicellular phenomenon is described which defines it and the same is considered here to discover the role of cellular events in transducing mechanical forces. For example, in a multicellular environment, responses of the cells play a key role in the maintenance and repair of damaged tissues. Such fine-tuning helped in sharing the mechanical load between the damaged cells and healthy cells that exist in the neighboring environment and participate in the underlying mechanism of the extracellular matrix (Figure 1).

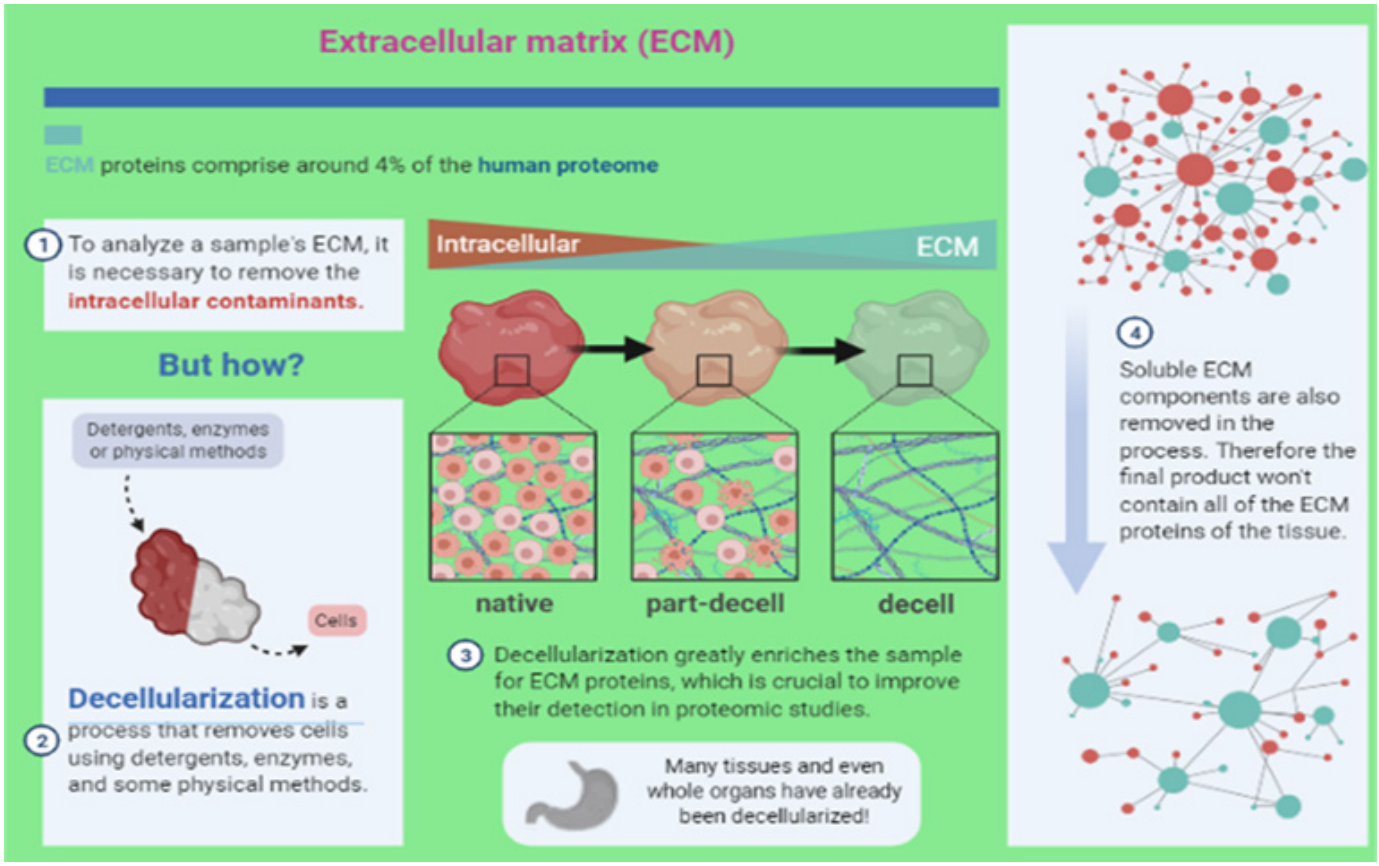

Figure 1: Schematic illustration of extracellular matrix. Biological interactions and designed tissue engineering can mimic the extracellular matrix components. Native, part-decell, and decell, "Adapted and created with permission from (biorender.com). Same is referred and acknowledged as per instructions".

The origin of such a micro-environment directly influenced the ability of a cell to sense mechanical happenings in these environments. It is a very well-known fact that the mechanotransduction pathways exist in the microenvironments, and any alternation in their mechanism-upset cell physiology and events including survival, shape, cell extrusion, cell intercalation, differentiation, migration [11]. Now, it is a quite clear fact that the nanotools and regenerative remedies should be re-designed as per the demand for multicellular assemblies, to have the ability to remodel accordingly. If any imbalance occurs between the architecture of these prescribed topologies and the multifunctional assemblies of nanoparticles during their implementation, then miscommunication will have happened in cell-to-cell relation. In the meantime, these events will initiate morphogenetic changes and influence cell functioning [12]. As a result, the remodeling of cell-cell junction, cell polarization, differentiation, migration, cell extrusion, and cell intercalation will be perturbed.

To fulfill the key aspects of the objective i.e., the formulation of preventing and regenerating therapeutics, there are unsolved scientific hurdles that exist and should be addressed. Hence, considering these routes at the time of designing the architecture of tissue engineering will lead to the formation of small tools in a novel way. Here, the main catalyst is nanomaterials that have the potential to boost the cell defense and concerned proceedings (mechanisms and cell signaling pathways) for preferential regulation of cell activities (behavior and differentiation). Using tissue engineering, nanoscale preventive, and regenerative medicines, the objective of cells and tissues repairing, restoring, and regenerating damaged components (blood vessels, lungs, and the heart) to be accomplished [13]. As already termed that the tissue engineering, nanotechnology, and medical biology are fulfilling the demands of innovation of biological subunits necessary for repairing, replacing damaged cells, tissue, and organs and enhancing their functioning to stimulate regeneration. For example, how cells are balancing with the mechanical force induced by neighboring cells and responding toward the transmit forces for processing and transforming the signals into chemical signals, are the hidden aspects of cell mechanotransduction types of machinery that to be analyzed.

Cadherin, Ca2+-dependent cell-cell adhesion proteins involved in cell adhesion processes at the adherens junction in a complex form and creating a multicellular environment for binding the cytoplasmic protein β-catenin [14]. This is an initiation process and moves forward by propagating the binding processes as per the mechanism wherein the cytoplasmic protein β-catenin fix binding adapter (filamentous-actin) (Figure 2).

The sequencing of binding keeps moving further till it binds adaptor protein α-catenin, and the main feature of it is to hunt vinculin. These routes keep proceeding until the origin of a new mechanical connection transpired between cell-cell adhesion proteins. The adhesion junction having a cadherin-catenin complex system and thus improve the features (dynamic and stability) of cell assembly [15]. The cadherin-catenin adhesion complex is also dependent on α-catenin because it senses force-dependent conformational changes in the regulation of protein interactions within the complex (Figure 3).

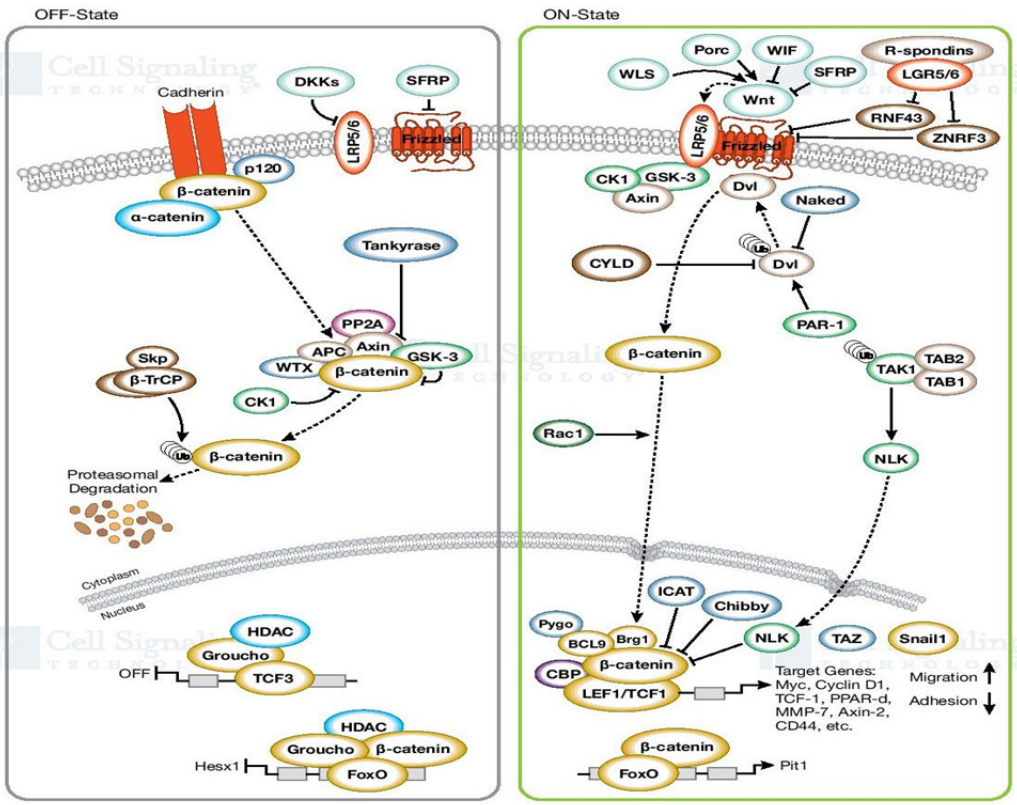

Figure 2: The conserved wnt/β-catenin pathway regulates cell fate decisions. This developmental cascade integrates signals of different pathways, including retinoic acid, FGF, TGF-β, and BMP, within different cell types and tissues. Activation of the wnt receptor and kinase GSK-3β from a regulatory APC/Axin/GSK-3β-complex. Wnt-signal (off-state), β-catenin, CK1, and the APC/Axin/GSK-3β-complex leading proteasomal degradation through the β-TrCP/Skp pathway. Illustration reproduced courtesy of cell signaling technology, Inc.

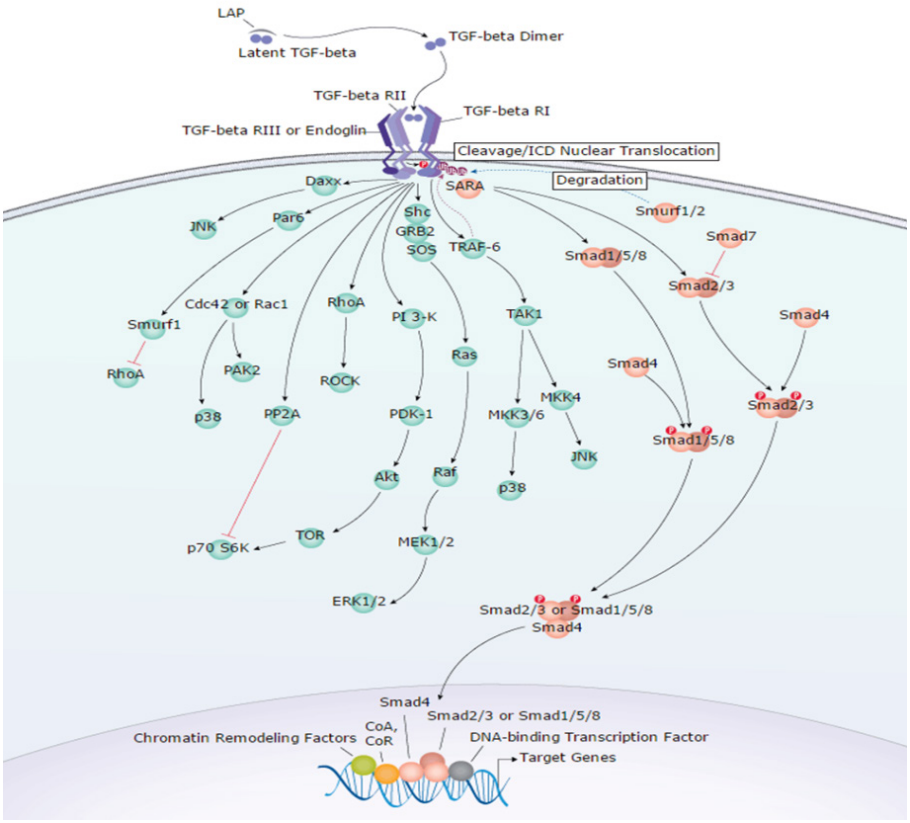

Figure 3: Transforming growth factor-β (TGF-β) signaling deals cell growth, differentiation, and development in biological systems. TGF-β signaling can also affect smad-independent pathways, including Erk, SAPK/JNK, and p38 MAPK pathways. Illustration reproduced courtesy of R and D system.

Hence, the chains of changes assist to cope up with environmental changes, mechanical contrarians, otherwise, there will be the start of deformation processes in the cellular structures. To make a change or to sense the transformation in enzymatic reaction or a protein-protein interaction, the cells only identified biochemical signals originated by deformations or conformational changes. The cell-cell or cell-extracellular matrix (ECM) -protein complex is performed as mechanosensors, which further senses the mechanical force and conformational changes and transforms it into biochemical signals (Figure 4).

Such, a lot of similar transformations happened simultaneously which were highlighted as cellular signaling pathways [16]. But, in ion channels, a conformational change can directly induce an enzymatic activity and this originates cell signaling and is reported in the literature as a tethered model. It is also identified that the lipid segment of the cell membrane can transform a mechanical force induced by conformational changes into biological signals and termed as a lipid bilayer model [17]. Therefore, the understanding of complex phenomena such as conformational changes, cellular pathways, and mechanosensing mechanisms, mechanotransduction, and extracellular matrix, enriches the strategies by filling the gaps and removing the hurdles coming in the implementation of perceptions of preventive and regenerative medicines. Dysregulation in these bio-machine chem-transformations leads to depositing extracellular matrix proteins. Therefore, it is a firm belief that it is the root of pathologies of aging and other fatal diseases. Hereafter, any dysregulation in cell mechanosensing generates complications on a large scale and damages the cell and tissues, and this situation forces the progression of pathologies. The diseased cells further stop the development of new cells/tissues as well as disturbing the functioning of the healthy tissues. The sense of cells or tissues is key for the smooth regulation of cellular functioning. Deviation in the sense to recognize mechanical and conformational issues, the cell lost control over proper channeling of ions, in these circumstances [18]. The ability of cells to act by biochemical signals, and respond accordingly toward the extracellular matrix for changes is the main causes behind it, which may initiate the pathogenesis of diseases. A need is there to understand the molecular mechanisms that happened in key adhesion mechanisms, and how they are involved in cellular sensing within the cell matrix is a key question that can be addressed soon for granting success to preventive and regenerative therapeutic. In this review, the author is analyzing the reported research findings related to the topics and discussing them in detail. The cellular mechanisms and processes of mechanotransduction, the mechanosensing, and signaling pathways are discussed by refereeing the related published research articles to summarize the reply to the questions as raised and outlined earlier. The mechanotransduction components such as the endothelial cells can easily sense the existing pressure in the blood flow [19]. The sensing abilities of endothelial cells and their capability to transform these mechanical forces into a flow of the blood or pressure into cellular signals are conferred and highlighted. These originated transmission signals modify the membrane potential and play a crucial role in the activation of the kinases that may initiate oxidation production. Later on, the oxidation mechanism initiates inflammatory signaling pathways [20]. At this time, it is coincidental to rheostat the initiation of diseases and then it can be prohibited from blocking the initiation stages of pathogenesis using nanoscale tools and devices having preventive and regenerative medicines as a component.

Again the emphasis must be focused to build checkpoints via nanodevices for controlling endothelial mechanotransduction and interrelated signaling pathways. In the presence of inflammation, the blood vessels scene pressure and initiate the generation of redox signals that amplified the oxidant concentrations. The interpretation of the blueprint of the mechanism between endothelial mechanotransduction signaling pathways and generation of redox signals may expose the inflammation processes that affect the whole mechanism, related schematic illustration displayed (Figure 5).

These findings will be the key to the successful implementation of preventive and regenerative medicines for the regeneration of injuries and wounded in the tissues, and organs [21]. The emergence of inflammation originated by mechanical pressure on endothelial machinery triggers the process of pathogenesis and it is a crucial finding and such cell activities must be a target for the newly developed nanodevices to perform as best regenerative medicines. It happened because their sizes perfectly matched with it and fulfill the needs of each other in the range of nano. With well-equipped features, these nanodevices play key roles and emerged as deciding factors for the successful implementation of regenerative therapy.

It was highlighted earlier that the extracellular matrix consisted and configured with the same scale components and matched perfectly with the architecture of the small tools. Nanodevices are carrying nanomedicine for delivery and can make their impact on cell behavior and cell differentiation processes via targeted drug delivery. Accordingly, the nanodevices are the main constituents in the designs and development of scaffolds and tissue engineering at the nanoscale. More, a need is there to outline the features of nanomaterials that can be utilized in improving damaged cell functioning, tissue growth, and stopping abnormal cell proliferation. Pro-inflammatory cellular insinuates neutrophils and macrophages in excess to interrupt healing in wounding [22]. The IL-1β and tumor necrosis factor–α (TNFα) disturbed the natural phenomenon of healing and enhanced the area of wound and injury. Because of these unnatural happenings, the concentration of metalloproteinase increased at the affected site that initiates the degradation of ECM, has the capability to impair cell migration and cellular events. The inflammasome is a component of the immune system, and the multiprotein complex originated during injury and wound is responsible for generating IL-1β within skin cell types. Meanwhile, the infection was initiated due to the existence of bacteria at the site. Infection supports the inflammasome and makes the situation worsen. The presence of the cytokine as a growth factor enhanced the normal wound healing process by initiating an anti-inflammatory response and environment (Figure 6).

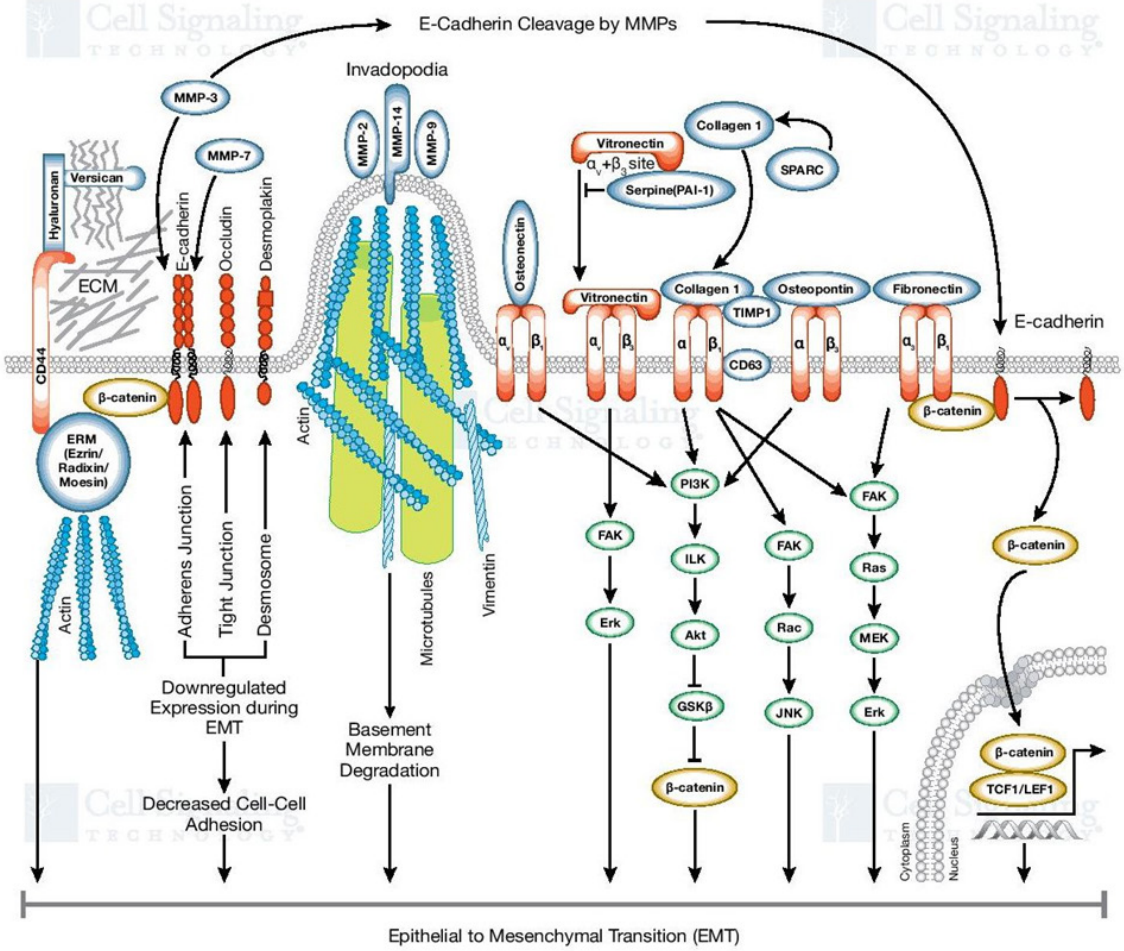

Figure 4: Illustration showing extracellular matrix. Dysregulation in cell mechanosensing, complications and forces the progression of pathologies. Deviation in mechanical and conformational issues, proper channeling of ions, biochemical signals, and respond to extracellular matrix changes. Initiate the pathogenesis of the diseases. . Illustration reproduced courtesy of cell signaling technology, Inc.

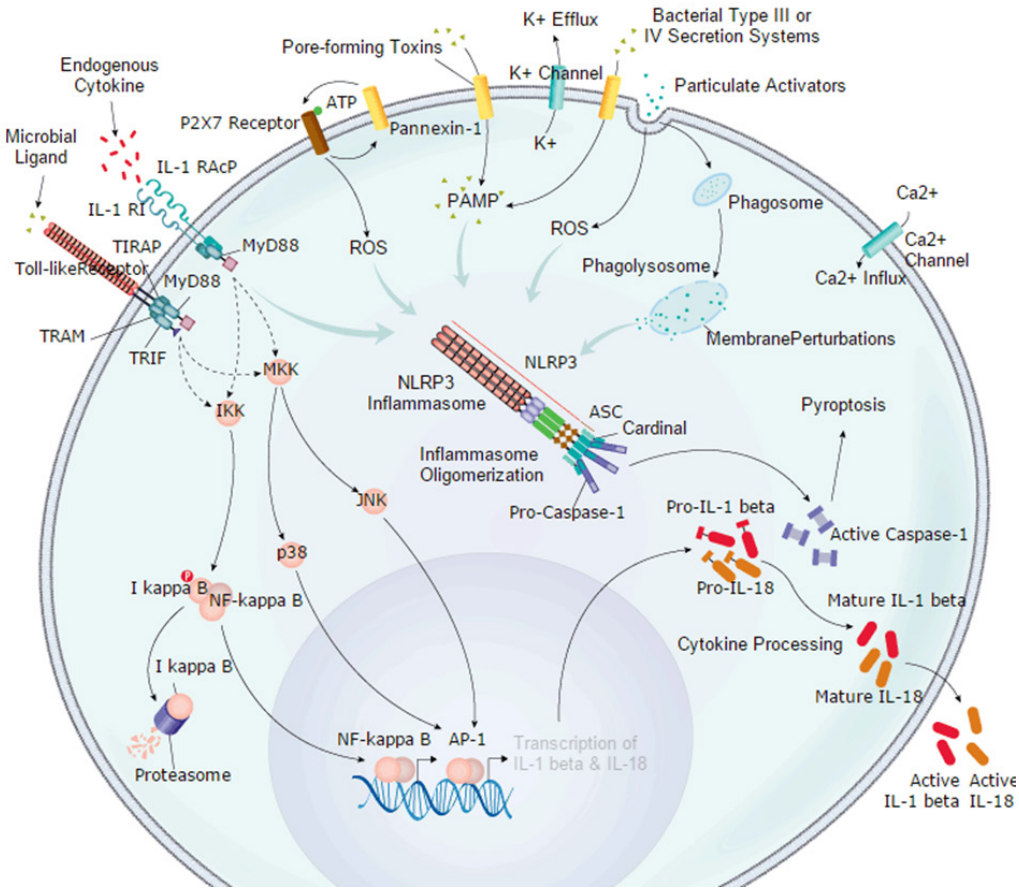

Figure 5: Inflammasome illustration reproduced courtesy of R and D system. Proinflammatory cytokines IL-1 and -18, control metabolic enzyme expression, pyroptosis, phagosome maturation, and vasodilation an inflammatory programmed cell death. Inflammasome signaling initiates autoimmune disorders.

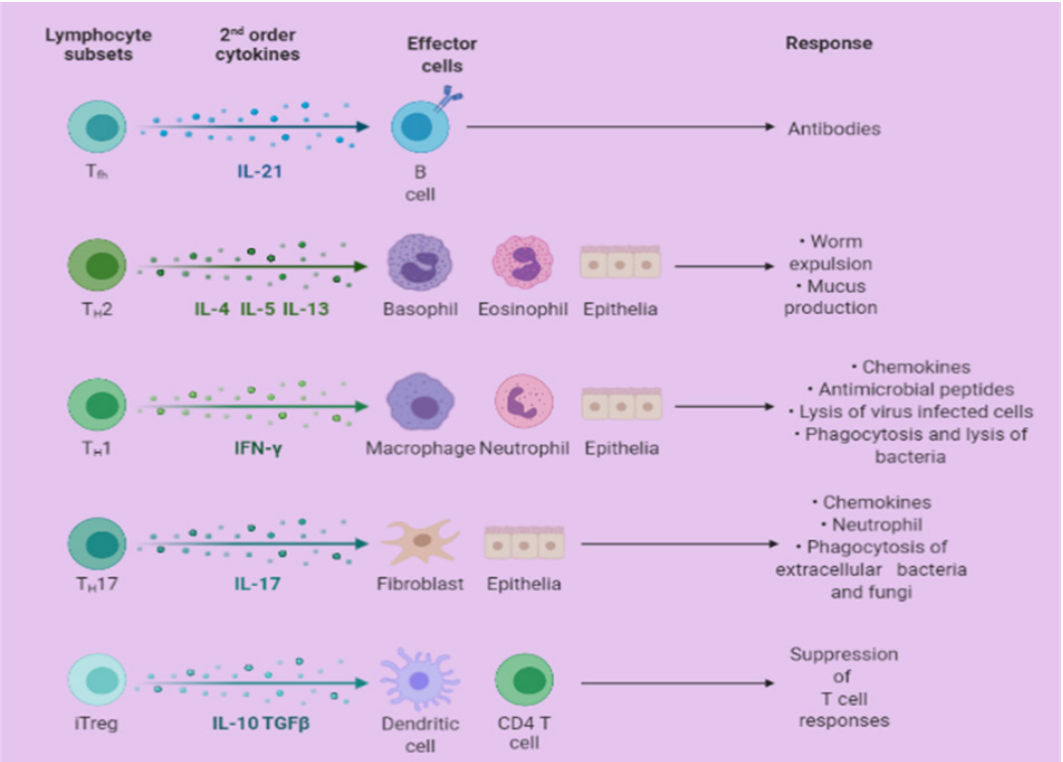

Figure 6: Schematic illustration of generating IL-1 within skin cell types. "Adapted and created with permission from [biorender.com]. Same is referred and acknowledged as per instructions".

Besides it, wound infection promotes the expansion of chronic wounds. By inhibiting the growth of microbes, the epidermis of the skin secretes antimicrobial peptides and stop damages that come into existence due to exposure to microbes. The presence of polymicrobial at the site of the wound disturbs the defense responses and delays healing. Therefore, a deeper understanding of these cellular events further exposes the routes of inflammatory response and impact in healing.

SMALL TOOLS AND NANO-BIO INTERFACE FOR STIMULATION AND REJUVENATION

Proper care of biological systems through the use of tools of nanoscale size has empowered researchers in controlling the mechanistic aspects of cellular machinery. Various reports have highlighted the use of nanotechnologies in the field of caring, preventive, and regenerative medicine [23]. Reported nano-biomimetic, used as nano scaffolds, and tailored at the molecular level and showed promise for nano/micro tissue regeneration. The importance of framing, porosity, and bio-functionality of these scaffolds matters while creating for the development of nanotools for application in preventive and regenerative medicines. Special emphasis is kept on the synthesis, characterization, and functional abilities of these nanodevices which decide their importance in the propagation of the tissue regeneration process and mimicking of the extracellular matrix of vascular and cartilage tissue for the transportation of metabolites and nutrients. Need for analysis of natural extracellular matrix and further utilization in the designing of biomimetic biomaterials [24]. The effort has been to incorporate a nanofibrous matrix and cell seeding can be achieved by electrospinning nanotechnology. These developed nanofibers have the potential to use for the creation of blood vessels and nerve regeneration. The biomimetic nanocomposite of self-assembled collagen and minerals can also be applied in the field of tissue engineering. Highlighted the challenges in generating tissues or organs that mimic the cellular compartment. His team pushed the thought further for the requirement or to achieve fabrication layer-by-layer during tissue engineering by using the laser, micro-molding, and electrospinning-based techniques [25]. This must be structured with outstanding geometric precision, the formation of interconnected, functional, and perfused vascular networks for proper functioning at the cellular level. Shaochen with his research collaborators opens new frontiers by proposing three-dimensional (3D) structures that can be utilized precisely for engineering the architecture and topography of scaffolds for porosity, cellular interactions, and mimics the microarchitecture of tissues [26]. His team underlined the finding based on immunohistochemistry results, confirmed that the scaffold holds their endothelial phenotype during biological functionality as micro-fabricated scaffolds.

Explored the endothelial cells that have abilities to form new vessels and define it as neoangiogenesis [27]. Ali Khademhosseini co-workers discussed the fabrication of nanomaterials by different techniques such as electrospinning, nanolithography, and self-assembly make them highly capable of the regeneration of various tissues and organs (blood vessel, bone, muscle, cartilage, heart, and bladder tissue) [28]. Laurencin et al. reviewed the role of biomaterials in regenerative techniques to elucidate the new design of biomaterials for bone regenerative engineering [29]. Reported that nano-composite scaffolds within 3D printed constructs employed multiple external physical stimuli representing an additional tool for healthcare applications [30]. Jabbari et al. Reported the natural hydrogels with the strongly solvating, reducing, and stabilizing agents, that can be converted into injectable hydrogels for effective use in tissue engineering and regenerative medicine [31]. Kaushik et al. expressed the concept of biocompatibility and suggested that there is a requirement for shaping the properties of materials synthesis, surface functionalization, and functionality, and later on, these nano-bio materials can be used as bioactive and biodegradable materials for treating severe injuries and diseases surrounded by tissues [32,33]. PX expressed the role of biomaterials as pivotal scaffolds that provide three-dimensional templates and synthetic extracellular matrix environments for tissue regeneration to mimic certain advantageous characteristics of the natural extracellular matrix, or developmental or wound healing programs [34]. Zhao et al. reported that graphene from nano-composites with other materials can provide exceptional platforms for both stimulating neural stem cell adhesion, proliferation, differentiation, and neural regeneration [35]. Alarcon et al. expressed that unique properties of nanomaterials can be useful for the synthesis of bio-inspired hybrid/composite materials, which evidenced improved regenerative properties, as well as electrical conductivity and antimicrobial properties [36]. Tissue engineering has the potential to revolutionize the healthcare industry [37]. Nanofibrous scaffolds incorporation of other components, including other nanofeatures into the scaffold structure well-designed nanofibrous scaffolds, can be mimicking the cellular structure. These composite scaffolds showed a decrease in the incidence of apoptosis. Ramakrishna et al. presented spinning methodologies to fabricate nano-scaffolds. Hence, nano and microscale technologies have been emerging in creating a niche for tissue regeneration and regenerative medicines, creating unprecedented topography and surface treatments [38]. Some suggested using nanotopography that tissue regenerate and activate natural tissue functions upon transplantation [39]. Cheon et al. suggested that the regeneration of the healthy and injured tissue is enhanced by nanostructures, for example, the regeneration of the endodontics achieved by the pulp-dentin tissue [40]. Rahuman et al. expressed that the application of nanotechnology to stem-cell biology could address the challenges of disease therapeutics and should be utilized for the development of regenerative therapy [41,42]. Webster et al. discussed that tissue engineering and the emergence of nanotechnology have increased tissue regeneration even on most rugged structures simply by mimicking the monofunctional features [43]. This can speed up various regenerative therapies, such as those for the bone, vascular, heart, cartilage, bladder, and brain tissue [44]. Ramezani et al. stated that emerging signs of progress in nanotechnology have resulted in the development of new materials, scaffolds, and drug delivery strategies to improve or restore the damaged tissues [45]. Xu et al. addressed that cell alignment uses tissue regeneration (e.g., neuron) and modulates mechanical properties of tissues, including the skeleton, cardiac muscle, and tendon [46]. PX et al. describe that nanostructured polymer scaffolds are the best option to use for tissue engineering and regenerative medicine. Zreiqat et al. utilized carbon nanotubes in bone tissue regeneration and engineering and further by evaluating the properties of carbon nanotubes with the nanoscale features that can direct their use in the extracellular environment [47]. Tal et al. reviewed the gold nanoparticle-integrated scaffolds useful for tissue engineering and regenerative medicine and also pointed out the methods used for creating tunable nanocomposite scaffolds with improved mechanical and electrical properties for tissue engineering [48]. Neves et al. used nanoparticles as bio-active agents to separate cells [49] (Table 1).

Table 1: Wound repair and regeneration: Materials and methodology.

Materials used	Methodology
Calcium-based Nanoparticles	Nanoparticles (NPs) consist of a hydroxyapatite core, to bind ions, proteins, and other organic molecules and can influence environmental calcium levels with the potential to modulate calcium homeostasis in vivo. PH-sensitive calcium-based nanoparticles and investigated their ability to enhance cutaneous wound repair [50].
Responsive 2D nanomaterials	Two-dimensional transition metal dichalcogenides such as molybdenum disulfide modulate and direct cellular functions of human stem cells through photothermal modulation. The global gene expression profile of stem cells reveals s significant influence on integrin, cellular migration, and wound healing by photothermal modulation of MoS2. The photostimulation of MoS2 may provide new approaches to regulate cellular migration and related functions [51].
Multidimensional nanomaterials	Current stem cell therapy suffers low efficiency in giving rise to differentiated cell lineages, which can replace the originally damaged cells. Nanomaterials provide unique physical size, surface chemistry, conductivity, and topographical microenvironment to regulate cell-cell and cell-ECM interactions. From three different nanotechnology families, three approaches are shown: (1) soluble microenvironmental factors; (2) insoluble physical microenvironment; and (3) nano-topographical features [52].
Scaffold micro-and nanostructures	nature of intercellular communication interlinked with growth factor (GF) and. complex scaffold micro-and nanostructures resembling that of natural extracellular matrix (1) describe non-cellular components of the wound environment that contribute to cutaneous tissue repair, (2) distinguish between different types of skin stem cells and their respective niches, and (3) describe how mechanical forces influence wound repair on the tissue, cellular, and molecular levels [53].
Nanocomposites	Such materials can improve several material properties, including mechanical stability, biocompatibility, and biological activity. The third section will deal with the emergence of a relatively new field of research using nanoparticles in advanced cell imaging and stem cell tracking approaches [54].
Green Peptide–nanomaterials	Developmental study on efficient wound care system where the possible use of natural peptides in combination with nanomaterials as tissue regenerating agents through an effective wound healing pathway [55].
Zinc sulfide nanoparticles	Zinc Sulfide nanoparticles (ZnS-NP) on wound healing in vitro with 2D and 3D models and in vivo with rat full-thickness wound model. ZnS-NP inhibited fetal bovine serum-stimulated rat skin fibroblast cell proliferation, altered cytoskeletal organization, and reduced collagen synthesis as well as contractile activity. ZnS-NP regulated redox homeostasis and promoted fibroblast viability in 3D hypoxia conditions. In the rat full-thickness wound model, ZnS-NP reduced wound contraction, enhanced re-epithelization, and promoted skin appendage formation [56].
Nanostructured scaffolds	Cell-cell and cell-matrix interaction in biological systems take place at the nanoscale level, the application of nanotechnology gives an edge in modifying the cellular function and/or matrix function in a more desired way to mimic the native tissue/organ. In this review, we focus on the nanotechnology-based recent advances and trends in regenerative medicine and discussed individual organ systems including bone, cartilage, nerve, skin, teeth, myocardium, liver, and eye [57].
Bioactive glass-gold nanoparticles ointment	Healing is a complex process in adult skin impairments, requiring collaborative biochemical processes for onsite repair. Diverse cell types (macrophages, leukocytes, mast cells) contribute to the associated phases of proliferation, migration, matrix synthesis, and contraction, coupled with growth factors and matrix signals at the site of the wound [58].
AgNPs size-, dose-, and time-dependent solutions	Cytotoxicity of AgNPs and propose the size-, dose-, and time-dependent solutions for reducing their cytotoxicity in wound care. This review will hopefully inspire the advanced design strategies of either dermal matrixes or wound dressings and their potential therapeutic benefits for chronic [59].
Metallic, ceramic, and carbon allotrope nanoparticles	Metallic, ceramic, and carbon allotrope nanoparticles have shown promise in facilitating tissue repair and regeneration. Inorganic nanomaterials have been employed to improve stem cell engraftment in cellular therapy, material mechanical stability in tissue repair, electrical conductivity in nerve and cardiac regeneration, adhesion strength in tissue approximation, and antibacterial capacity in wound dressings [60].
Nano-drug delivery systems	current nano-drug delivery systems holding pivotal potential for wound healing and skin regeneration, with a special emphasis on liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, nanofibrous structures, and nano hydrogel [61].
Biomaterials and theranostic nanoparticles	State-of-the-art materials, so-called 'smart' biomaterials, and theranostic nanoparticles. Nanotechnology-based therapy has recently announced itself as a possible next-generation therapy that can advance wound healing to cure chronic wounds [62].
Nanoscaffolds	They are ideal for topical delivery of drugs in a sustained manner, eliciting cell-to-cell interactions, cell proliferation, vascularization, cell signaling, and elaboration of biomolecules necessary for effective wound healing. Furthermore, nanoparticles can deliver one or more therapeutic drug molecules, such as growth factors, nucleic acids, antibiotics, and antioxidants, which can be released in a sustained manner within the target tissue [63].
Biodegradable hydrogel system containing curcumin encapsulated in micelles	A biodegradable in situ gel-forming controlled drug delivery system composed of curcumin-loaded micelles and thermosensitive hydrogel was prepared and applied for cutaneous wound repair. Furthermore, linear incision and full-thickness excision wound models were employed to evaluate the in vivo wound healing activity of Cur–M–H. In the incision model, Cur–M–H-treated group showed higher tensile strength and thicker epidermis. In the excision model, Cur–M–H group exhibited enhancement of wound closure. The histopathologic examination also implied that Cur–M–H could enhance cutaneous wound repair. In conclusion, biodegradable Cur–M–H composite might have great application for wound healing [64].

Stromal fibroblasts and the collagen-enriched ECM	Expression of MMPs by human corneal epithelial cells (HCECs) was affected both by the stromal fibroblasts and the collagen-enriched ECM they produce. In conclusion, and because of the many characteristics it shares with the native cornea, this human two layers corneal substitute may prove particularly useful to decipher the mechanistic details of corneal wound healing [65].
Hydrogel surfaces containing topographic features	Specific bio-ligands and developed an in vitro wound-healing assay. A potential benefit of restructuring and improving the surface of artificial corneas to enhance epithelial coverage and more rapidly restore the formation of a functional epithelium [66].
Au/g-C3N4 hybrid nanozyme	As common reactive oxygen species, H2O2 is widely used for bacterial inactivation and wound disinfection. The integration of AuNPs with ultrathin graphitic carbon nitride (g-C3N4) provides excellent peroxidase-activity, which can catalyze the decomposition of H2O2 to OH radicals much more efficiently, allowing the use of bio-safety levels of H2O2for the first time. More importantly, in vivo experiments indicate that our system could significantly prevent bacterial infections and accelerate the healing rate of wounds [67].
Glucocorticoid-loaded liposomes	The liposomes were loaded with the pro-drug dexamethasone-phosphate and surface-modified with either polyethylene glycol or phosphatidylserine. Fibroblast and keratinocyte cell cultures as well as a 3D skin equivalent model showed that liposomes applied locally to wounds are preferentially phagocytosed by macrophages. In particular, upon shell modification with phosphatidylserine, promote dexamethasone delivery to macrophages and induce a phenotype suitable to support chronic wound healing [68].
Gold–silver nanoshells	Gold-silver Nanoshells (AuAgNSs). With a strong response of the near-infrared laser due to surface plasmon resonance (SPR) from hybrid metallic nanoshell structure, AuAgNSs exhibits an efficient photothermal effect, and it simultaneously releases silver ions during laser irradiation to bacterial eradicate. In a chronic MRSA-infected wound mouse model, the AuAgNSs gel-mediated photothermal therapy/silver-release leads to a synergistic wound healing with negligible toxicity or collateral damage to vital organs [69].
KGM-modified SiO2 nanoparticles	Using a full-thickness excision model in either diabetic mice or healthy mice, the wounds treated with KSiNPs displayed a dramatically increased closure rate and collagen production, along with decreased inflammation and increased angiogenesis in the regenerating tissues. Based on these results, KSiNPs display great potential as an effective therapeutic approach for cutaneous wounds by effectively suppressing excessive or persistent inflammation and fibrosis [70].
Microporous nanocomposite hydrogels	Promising applications in promoting soft tissue regeneration. Air-in-water emulsion template that is stabilized by colloidal hybrids of carbon nanotubes (CNTs) and gelatin methacryloyl. Demonstrated appealing antimicrobial and wound healing performance [71].
Nano- and micro-fibrous scaffolds	Nano/micro-fiber-combined scaffolds have an innovative structure, inspired by extracellular matrix (ECM) that combines a nano-network, aimed to promote cell adhesion, with a micro-fiber mesh that provides mechanical support. Influence of this nano-network on the growth pattern, morphology, and inflammatory expression profile, expression of structural proteins, homotypic interactions, and angiogenic potential of human EC cultured on a scaffold made of a blend of starch and poly(caprolactone) [72].
Computer-designed nano-fibrous scaffolds	Fabrication of NF matrices while having precise control of internal pore size and structure, as well as external scaffold shape including architectures generated from computed-tomography scans and histological sections [73].
Calcium carbonate composite nano-fibers	To achieve mechanical stability of GBR membranes, composite nanofibers were spun on PCL nano-fibrous membranes which have high tensile strength, i.e., the membranes consist of two layers of functional layer (PCL/CaCO3) and a mechanical support layer (PCL) [74].
Scaffolds of nano-hydroxyapatite and silk fibroin	To promote bone regeneration mainly through signaling pathways associated with cell–biomaterial interaction. complemented our understanding of the underlying mechanisms of biomaterial osteoinductivity [75].
Silk based gold nano-composite conduits	Fabricated by adsorbing gold nanoparticles onto silk fibers and transforming them into a nanocomposite sheet by electrospinning. Pre-seeding the conduits with Schwann cells enhanced myelination of the regenerated tissue. Histo-morphometric and electrophysiological studies proved that the nanocomposite based conduits pre-seeded with Schwann cells performed best in terms of structural and functional regeneration of severed sciatic nerves [76].
Nano-engineered in situ forming composite hydrogel	Hydroxyapatite enriched in situ forming hydrogel shows osteogenic potential. The osteochondral hydrogel was developed by the integration of subchondral and chondral hydrogel layers with a gradient interface. Osteochondral hydrogel promoted the regeneration of hyaline cartilage and mineralized subchondral bone [77].
Micro/nano hybrid-structured biphasic calcium phosphate bioceramics	biphasic calcium phosphate (BCP) bioceramics composed of micro-whiskers and nanoparticles hybrid-structured surface (hBCP) were fabricated via a hydrothermal reaction. The in vivo long bone defect model of beagle dogs implanted with hBCP bioceramics achieved a higher quality regenerated bone as compared to the traditional smooth-surface BCP control group [78].
Magnetic field and nano-scaffolds	Current developments in magnetic strategies to improve the cells, scaffolds, and growth factor deliveries were described. The magnetic-cell strategies included cell labeling, targeting, patterning, and gene modifications. MNPs were incorporated to fabricate magnetic composite scaffolds, as well as to construct delivery systems for growth factors, drugs, and gene transfections [79].
Multiphasic microgel-in-gel materials	Tunable microgel-in-gel materials are reported that build on a versatile platform of multifunctional poly(ethylene glycol)-heparin gel types and integrates monodisperse, cell-laden microgels within cell-laden bulk hydrogel matrices. By choosing the structure and composition of the microgel and the bulk gel compartments independently, our micro gel-in-gel arrangements provide cross-scale control over tissue-mimetic features and pave the way for culture systems with designed microenvironmental characteristics [80].

Biomimetic cell-derived nanocarriers	Biomimetic cell-derived nanocarriers may achieve different specific biological effects due to the benefit from their host attributes. In this review, we introduce the technologies that are under extensive investigation, including extracellular vesicle-based formulation technology and cell membrane coating technology [81].
Self-healing nanocomposite hydrogels	Bone tissue engineering based on stem cells, growth factors, and bioactive scaffolds present an appealing but challenging approach for the rehabilitation of patients with bone defects. non-invasive delivery system based on injectable and self-healing nanocomposite hydrogels for sustained protein release, which has the potential to improve the current orthopedic strategy [82].
Rebamipide-loaded chitosan nanoparticles	Rebamipide RBM-loaded chitosan nanoparticles (RBM/CTS NPs) were prepared using the ionic cross-linking method. Physicochemical characteristics and the wound healing promotion effect, as well as in vitro influence on macrophages were evaluated [83].
Hydrogel based on chitosan/oxidized konjac glucomannan/AgNPs	Self-adapting hydrogels that are adhesive, injectable, and self-healable are being developed to efficiently treat irregular skin wounds. Here, we present an approach based on dynamic Schiff-base bond formation to prepare self-adapting hydrogel dressings that automatically adapt to irregular wounds under natural conditions and sustain total contact with the injured site [84].
Polysaccharide-based hydrogels	Polysaccharides possessing distinctive properties such as biocompatibility, biodegradability, and nontoxicity are promising candidates to structure hydrogels for wound healing. Polysaccharide-based hydrogels can provide suitable moisture for the wound and act as a shield against bacteria [85].
Injectable hydrogel systems	Injectable biomimetic hydrogels composed of silk nanofibers (SNF) and hydroxyapatite nanoparticles (HA), deferoxamine (DFO), and bone morphogenetic protein-2 (BMP-2) were loaded on SNF and HA to introduce more angiogenic and osteogenic cues. The angiogenesis and osteogenesis capacity of injectable hydrogels could be regulated by tuning the delivery of DFO and BMP-2 independently, resulting in vascularization and bone regeneration in cranial defects [86].
Core-shell particles for drug-delivery	Core-shell structures incorporating payloads such as drugs, peptides, or hormones have been investigated in pre-clinical studies. The present review describes the state-of-the-art techniques for designing core-shell particles for biomedical applications [87].
Liraglutide-loaded PLGA/gelatin electrospun nanofibrous mats	The effects on diabetic wound healing, vascularization, and its underlying mechanism were evaluated. The results revealed that PLGA/Gel/Lira remarkably improved the healing efficiency of diabetic dermal wounds characterized by shortened wound closure time, increased blood vessel density, and elevated collagen deposition and alignment [88].
Reactive oxygen species-inducing nanoparticles, and stem cells to promote angiogenesis	Classified into two categories as (1) use of growth factors, reactive oxygen species-inducing nanoparticles, and stem cells to promote angiogenesis, and (2) in vitro or in vivo revascularization of skin grafts. This review summarizes the state-of-the-art approaches, their limitations, and highlights the latest advances in therapeutic vascularization strategies for skin tissue engineering [89].
Inhibitor from bionic scaffolds	Small molecule-loaded bionic scaffolds have a promising future in skin tissue regeneration. Small molecules such as deferoxamine (DFO) have been released slowly from silk hydrogels and stimulated angiogenesis and wound healing, but failed to achieve functional recovery of the skin [90].
Nanomaterials in 3D step-gradient nanocomposite hydrogels†	3D network of the step-gradient NC scaffolds provides sustained release of bioactive molecules, which is beneficial for local drug delivery applications. We demonstrate that bifunctional NMs used in vertically increasing concentrations can influence the migration of cells in the XZ plane of the step-gradient NC scaffolds [91].
Magnesium hydroxide nanoparticles	Fibroblast-derived extracellular matrix (ECM)-supported scaffolds made up of poly(lactic-co-glycolic acid) were prepared with the enhanced preservation of ECM components by composites with magnesium hydroxide nanoparticles (MH NPs) and were applied for the renal tissue regeneration [92].
Dual-responsive biomineralized polydopamine–calcium phosphate nanocomposites	Dual pH/thermal responsive biomineralized nanocomposites (PCNPs) were rationally designed and prepared based on the hierarchical assembly of calcium phosphate (CaP) and polydopamine (PDA). Third, the autophagy inhibitor chloroquine (CQ) was absorbed onto the surface of PDA via non-covalent interactions, forming PCNPs/DC. CQ was the only FDA-approved autophagy inhibitor in clinical trials that could inhibit autophagosome fusion and degradation [93].
Micro- and nano-bubbles	Micro- and nano-bubbles (MBs) have been developed as vehicles for detection, investigation, and drug delivery, specifically targeting atherosclerotic sites. The assembly process involves some specific substrates (proteins, lipids, and polymers) [94].
Graphene oxide nanosheet-reinforced chitosan scaffold	Fabricate synthetic bone scaffolds with biocompatibility, suitable mechanical properties, antibacterial ability, and osteoconductivity [95].
Thrombin-responsive engineered nano excavator	The resulting microbubbles enable real-time monitoring of the therapeutic process with ultrasound imaging and high-performance photoacoustic imaging after loading DIR. This non-invasive nanopharmaceuticals thrombolytic strategy is an improvement over existing clinical methods without systemic side effects [96].
Nano thin, nanoporous poly(lactic-co-glycolic acid) membrane	Nano thin, nanoporous poly(lactic-co-glycolic acid) membrane and cell sheets were laid layer-by-layer and revascularized with endothelial cells between the layers and reduction in adverse cardiac remodeling post-myocardial infarction in vivo mimicking direct cardiac reprogramming and revascularization [97].
Scaffold-microfiber/nanofiber core-sheath yarns	Fabricate a novel knitted tendon scaffold made of microfiber/nanofiber core-sheath yarns and evaluate the biocompatibility and the effect of tenogenic differentiation and tendon tissue regeneration in vitro and in vivo [98].

Elizabeth et al. noted that fiber-reinforced scaffolds can be used for the formation of nanofibrous arrays capable to mimic original tissues for restoring concerned functioning [99]. Liu et al. detected structural features of scaffolds applicable in cell engineering [100]. Mauck et al. expressed that nanofibrous scaffolds for soft tissue engineering and regeneration and reviewed the perspective on current processes and procedures in creating and utilization of nanofibrous structures and also suggests the futuristic applications [101]. Kong et al specified the interfacial tissue engineering of the heart by regenerative medicine derived from soft cell-porous scaffolds that helped improved the engraftment and retention [102]. Massimo et al. recommended a new range of scaffolds for alveolar bone regeneration and reviewed the different nano-scale scaffolds and discusses the factors of tissue engineering for alveolar affect bone regeneration [103]. Zhang et al. pioneered bone tissue regeneration by using the scaffold microenvironment influences [104]. Some of the properties of these scaffolds also described the special emphasis on the surface topography. Lin et al. underlined a novel multifunctional carbon aerogel-coated platform for enhanced bone regeneration and tissue regeneration [105]. Using nanotopography and nanokicking for regenerative medicine (tissue regeneration) enhanced bone generation.

CONCLUSION

Nanotechnology emerged as the best tool in the development of preventive and regenerative therapeutics that can enhance cell mimicking, reinforcing the path of signaling defects, and regenerate cells and tissues. To replace a functioning tissue or organ is still beyond the approach and to have control at the atomic, molecular, and supramolecular levels, nanoscale devices, and small tools should be designed in such a way that they can fulfill the needs to achieve the target. It is also a necessity to know how do nanoscale devices perform different functions at the nanoscale and authorize the nano-bio interface to upgrade cellular matrix and interrelated interactions. Recently, the developed nanoscale scaffolds were used for tissue engineering in various fields (neurology, cardiology, orthopedics, and skin tissue regeneration). As, the injuries create a defect in axonal junctions in the spinal cord and disturb neuronal functioning, and further, it hinders the regeneration of damaged tissue. The regenerative nanodevices fill up existed gaps in the neurons by delivering regenerative drugs, and if the drug delivery is perfect and delivered at the affected region, it will inhibit apoptosis, and infection first, and then will treat the damaged area. The key features of nanodevices are to promote neurogenesis, axonal growth, and angiogenesis. These features are underlined as therapeutic proficiency. These nanodevices are also effective and have variously applicable in other categories of healing remedies such as diagnosis, drug delivery, tissue engineering, and cell therapy. Being a biocompatible nanomaterial, the graphene-based materials were also revealed medicinal features at the time of development of engineered scaffolds applied for tissue regeneration. The 3D graphene-based scaffolds displayed potential in mimicking the cellular activities. But, graphene-based nanomaterials and other multifunctional nanomaterials are used in tissue engineering and regenerative therapy as a potential material. Many other medical complications persisted in the field of regeneration therapy and were well discussed in the literature. The success of these strategies depends on their potential and performance as targeted/stimuli-response delivery agents, and nanoscale devices offered to control cell behavior efficiently. The architectures and assemblies of nanotools and devices at nanoscale enhanced cellular events extracellular matrix, and signaling pathways including cellular mechanotransduction, cell-cell, and cell-ECM interactions. These are the key component of cell mechanotransduction machinery, and any imbalance in their regurgitation promotes signaling defects. These consequences arose because of the signaling defects in healthy tissue and naturally originated repair response, including inflammation, angiogenesis, matrix deposition, and cell recruitment. Biomaterial substrates can be engineered to initiate topographical signals to cells via a nano-bio interface, the cellular and molecular mechanisms underpinning tissue control key cellular processes and guide cell fate decisions. After considering the needs of cell mechanotransduction phenomena, a lot of nano-bio tools and devices were designed for originating novel nano-bio interfaces that can be applied to have an influential regenerative route. The biocompatibility of nanoscale nano-bio tools and devices derived from multifunctional materials depends on the compositions of components (collagen, fibrin, elastin, chitosan, silk fibroin, chitin, gelatin, and fibrinogen) and used in manufacturing and to enhance the efficiency and effectiveness of nanotools and devices which are prepositionally interlinked with the physical parameters of these materials (stiffness, nanofibers, nanotubes, nanoparticles, structure, flexibility, pore size, and ligand density).

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