BIOCELL
2023 47(4): 789-808

Tech Science Press

Understanding cell-extracellular matrix interactions for topology-guided tissue regeneration

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Key words: ECM, Stress, Mechanical force, Scaffold, Mechanotransduction, Tissue engineering

Abstract: Tissues are made up of cells and the extracellular matrix (ECM) which surrounds them. These cells and tissues are actively adaptable to enduring significant stress that occurs in daily life. This astonishing mechanical stress develops due to the interaction between the live cells and the non-living ECM. Cells in the matrix microenvironment can sense the signals and forces produced and initiate a signaling cascade that plays a crucial role in the body's normal functioning and influences various properties of the native cells, including growth, proliferation, and differentiation. However, the matrix's characteristic features also impact the repair and regeneration of the damaged tissues. The current study reviewed how the cell-ECM interaction regulates cellular behavior and physicochemical properties. Herein, we have described the response of cells to mechanical stresses, the importance of substrate stiffness and geometry in tissue regeneration, and the development of scaffolds to mimic the nature of native ECM in 3D for tissue engineering applications has also been discussed. Finally, the study summarizes the conclusions and promising prospects based on the cell-ECM interplay.

Introduction

Multicellular organisms like humans comprise billions of cells, each serving a specific function in the body's normal functioning. The interaction between cell to cell and cell to the matrix is crucial to acquire any function. Cells must communicate with the surrounding environment to feed, proliferate, and differentiate. To accomplish this, they should be able to recognize the characteristics of the environment they are living in. Cells can sense the chemicals in their surroundings and respond to them in continuation of the various tasks in the body. During growth and development, cells experience many physical changes such as shear, stretch, and compression. For example, while walking or running, cells in the musculoskeletal system confront mechanical forces, and such cells are referred to as mechanosensitive cells (Evans and Gentleman, 2014; Schwander *et al.*, 2010). An extracellular matrix (ECM) is a three-dimensional network of proteins and other molecules that supports and surrounds the cells inside the body. It is a non-cellular structure that supports tissues and organs. ECM proteins, growth factors, cells, and other substances present in niches help cells exhibit specific structures and functions at nano-, micro-, and macro-scales (Schenke-Layland *et al.*, 2011). It offers various signaling cues that control cell proliferation, differentiation, and adhesion (Huang and Li, 2011). How cells communicate with the ECM and its proteins varies depending on their position. Individual cell types have different anchoring connections between cells and the ECM. Mesenchymal stem cells use adherent junctions to adhere to the encircling ECM, while the epithelial cells are anchored to the ECM via hemidesmosomes. Integrins are cell surface receptors involved in the interaction between cells and ECM. These integrins are heterodimers and serve as transmembrane connectors (Alberts *et al.*, 2002). By structural changes and variations in the binding affinities of integrins, cells may detect and react to the mechanical stresses from the ECM (Puklin-Faucher and Sheetz, 2009). The study of how cells produce and perceive physical and mechanical forces is known as mechanobiology (Ruiz and Chen, 2007). Cell growth, development, homeostasis, and tissue remodeling are, however, influenced by it (Ethier and Simmons, 2007). Various environmental conditions exhibit a shift in cell behavior in 3D culture compared to 2D monolayers. Therefore, it is feasible to control cellular behavior, leading to morphological features that take place *in vivo*, if the cell microenvironment *in vivo* can be imitated

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Received: 24 August 2022; Accepted: 15 November 2022

Doi: 10.32604/biocell.2023.026217

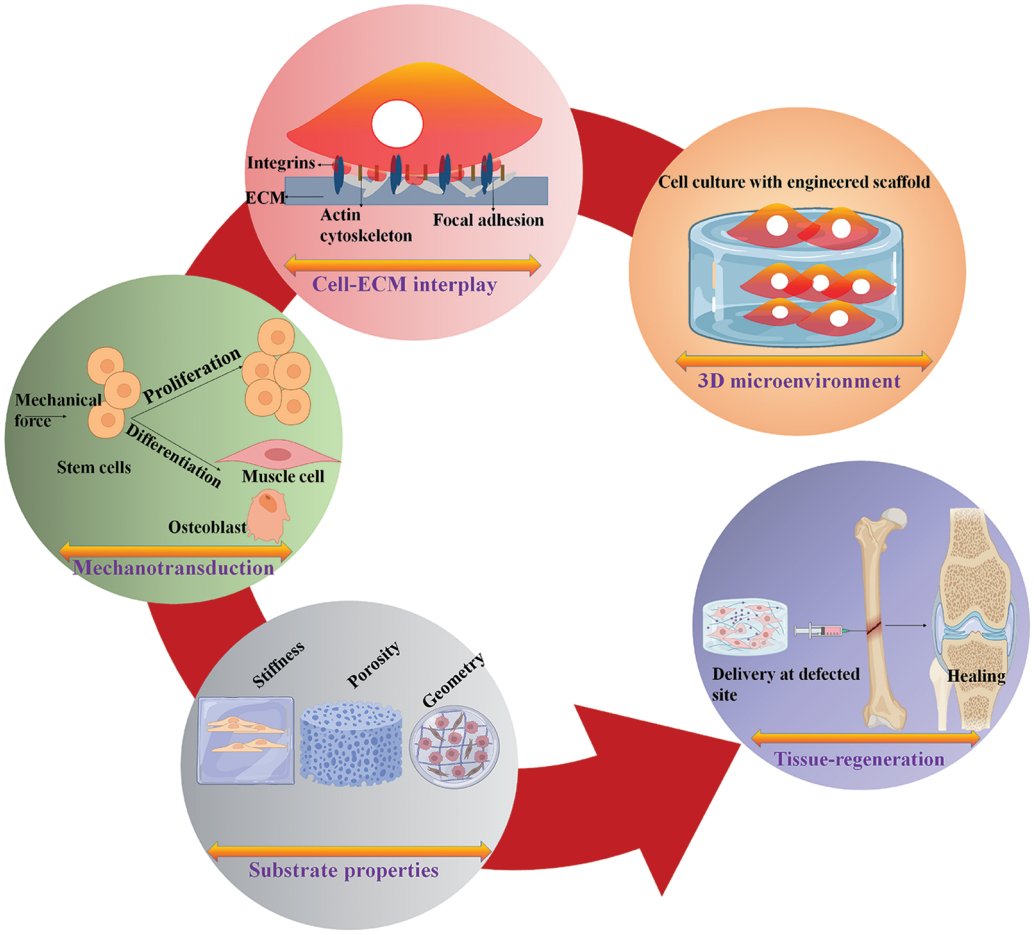

FIGURE 1. Schematic representation of cell-matrix interactions and their influence on cell behavior and the development of scaffolds for tissue engineering applications.

in vitro (Hussey *et al.*, 2018). Aggregating 3D cells or cell suspension in 3D hydrogels comprised of ECM proteins can induce this imitation (Antoni *et al.*, 2015; Edmondson *et al.*, 2014; Langhans, 2018; Parrish *et al.*, 2018). The "outside-in" and "inside-out" signaling mechanisms that define a cell and ECM are controlled by geometric and molecular requirements. The architecture of cell-cell and cell-matrix, and signaling molecule's distribution, is influenced by variations in the extracellular environment of the cells (Lee and Vasioukhin, 2008; Morrison and Kimble, 2006; Wodarz and Näthke, 2007).

The cell-matrix communication in tissue repair is becoming increasingly important because mechanobiology-derived scientific advancements in scaffold design methods provide information on the natural and essential cues to facilitate tissue regeneration. This study illustrates the regulation of cellular behavior due to the cell-matrix interactions—impact and importance of substrate characteristics such as stiffness in cell proliferation and differentiation. Furthermore, developing scaffolds with tunable properties to regenerate damaged tissues is also discussed. Fig. 1 represents a schematic overview of the present study.

Cellular Response to Mechanical Forces

Cell mechanics

The core of a cell contains a fluidic material packed with various macromolecules, organelles, and components that carry out various processes. The higher-order bundles and meshes are made up of filament networks called the cytoskeleton, which gives cells the potential to withstand extrinsic mechanical stress (Moeendarbary and Harris, 2014). As illustrated in Fig. 2a, microtubules, actin filaments, and a collection of polymers called intermediate filaments are the three primary categories of cytoskeleton polymers. These polymers interact together to regulate the mechanics and morphology of cells. The three cytoskeleton polymers play a crucial role in regulating cell integrity and are arranged into networks that withstand distortion and rearrange in response to external stimuli. When actin filaments and microtubules are polymerized and depolymerized, specific forces are produced that cause alterations in the shape of cells by motor proteins that migrate along the microtubules and actin filament to govern the arrangement of cell constituents (Fletcher and Mullins, 2010). Actin filaments are ~20 μm long, semiflexible, and dynamic, allowing cells to move and alter their shape (Gittes *et al.*, 1993). Single filament stiffness does not significantly impact the actin cytoskeleton's potential to resist the mechanical force; instead, resistance to mechanical force is a result of a highly organized structure that these filaments create and the associated connections with the polymerizing agents and crosslinkers. The actin cytoskeleton, for instance, creates a thick mesh of 200 nm beneath the apical cell membrane that contributes to the mechanical integrity of the cell, basal fibers bind to the linear bundles, and ECM regulates and maintains stress across the intracellular

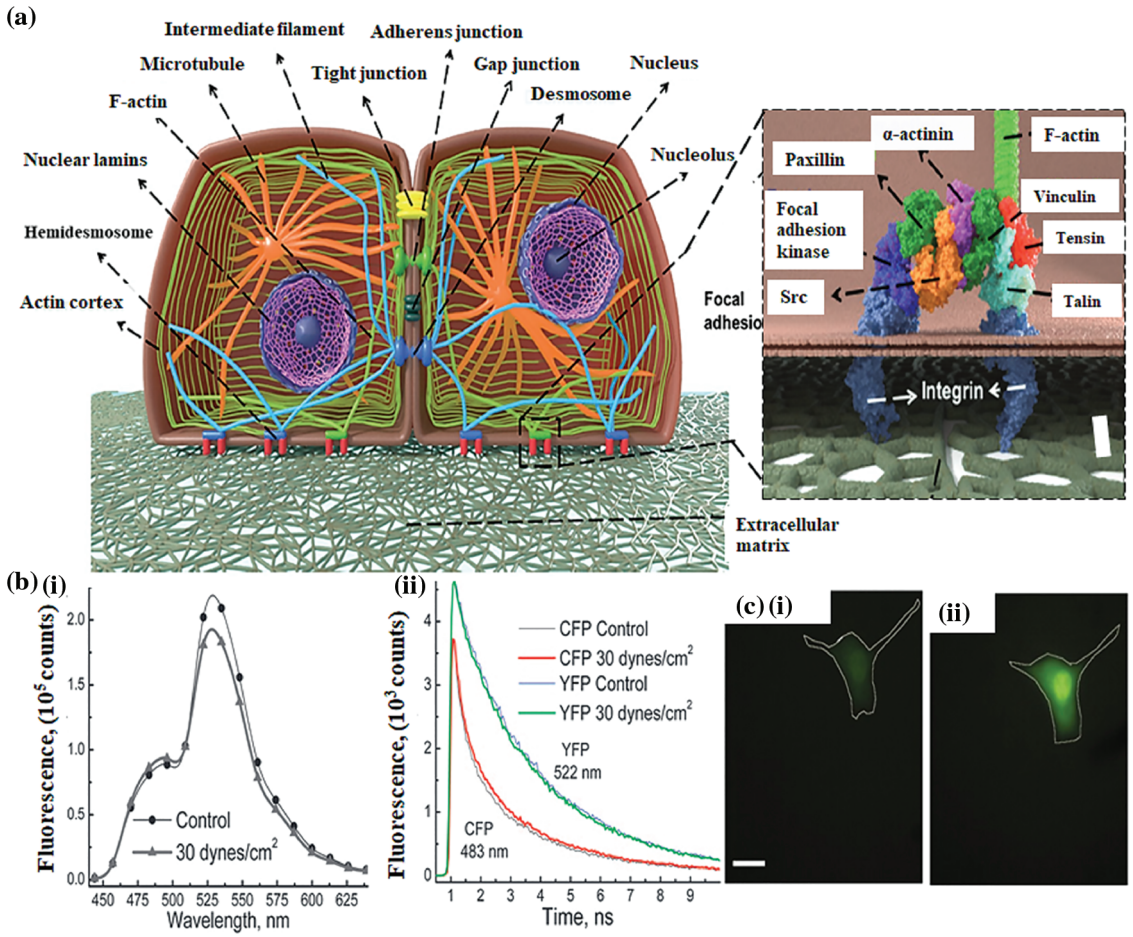

FIGURE 2. (a) A schematic illustration of the cellular cytoskeleton (architecture of cell-cell junction and focal adhesion proteins involved in the cell-ECM interactions) (Septiadi *et al.*, 2018); (b) (i) Fluorescence spectra of B2K G-protein receptor prior to and after 2-min of stimulation by shear stress (ii) Fluorescence degradation dynamics of the receptor proteins in response to the fluid shear stress (Chachisvilis *et al.*, 2006); (c) Effect of stretching on the intracellular concentration of calcium ions (i) Fluo-4 dextran intensity before loading the stretching force (ii) 10 min after loading the stretching force (Munevar *et al.*, 2004).

junction (Moeendarbary and Harris, 2014). Microtubules are rigid polymers and possess challenging assembly kinetics. Microtubules can collapse under the compressive stresses in cells; the length of a microtubule is an estimate of flexibility that improves with rigidity and it corresponds to a persistence length of ~5 mm (Brangwynne *et al.*, 2006). In the interphase of the cell cycle, when cells become ready for division, cells make use of the rigidity by forming radial patterns of microtubules that serve as an important center for the intracellular movement.

Actin filaments and microtubules are both polar and possess structural asymmetries in their subunits on a molecular basis. Due to their polarity, both actin filaments and the cytoskeleton function as tracks for motor proteins that travel in a single direction. Dynein and kinesin are motor proteins for the microtubules, while myosin proteins function as motor proteins for the actin filament. These motor proteins are crucial for the organization of the actin cytoskeleton and microtubules and play a significant role in cell mechanics. Microtubules and actin filaments are substantially longer than intermediate filaments; intermediate filaments are categorized as elastic polymers (Gittes *et al.*, 1993; Mücke *et al.*, 2004). They are the least rigid type of cytoskeleton filament and are preferable for resisting tensile stress. Intermediate filaments can form crosslinks with the other filaments, namely, microtubules and actin filaments, via plectin protein (Wiche, 1998). Intermediate filaments can be found in the cytoskeleton and the nuclear envelope, providing structural support to cells (Buehler, 2013). Different adhesion complexes are physically associated with the intermediate filaments. For instance, vimentin intermediate filaments link to integrins directly via connecting to β3 cytoplasmic tail and through bullous pemphigoid antigens 1 and 2 (BPAG) plectin linker proteins by establishing dynamic interactions with plakin repeat motifs (Bhattacharya *et al.*, 2009; Fogl *et al.*, 2016; Kim *et al.*, 2016). In response to external mechanical forces, various cell types generate intermediate filaments; lung epithelial cells generate a network of keratin intermediate filaments that enables the cells to sustain shear stress (Flitney *et al.*, 2009). Intermediate filaments are essential for arranging intracellular organelles and help maintain the cell's mechanical integrity. Vimentin is a key element influencing the localization of the Golgi complex, mitochondria, nucleus, and endoplasmic reticulum directed by actin and Rac1 (Dupin *et al.*, 2011; Gao and Sztul, 2001; Guo *et al.*, 2013; Matveeva *et al.*, 2015; Nekrasova *et al.*, 2011).

Mechanical forces are essential in balancing the body's normal functioning and pathophysiology. Various forces, such as compressive, shear, or tensile stress, based upon the cell type, exert their effect on cellular events, for example, cellular differentiation, proliferation, synthesis of proteins, and growth factors. Different types of cells in the body respond to these mechanical forces and are termed mechanosensitive cells, including fibroblasts, tenocytes, chondrocytes, and endothelial cells (Wang and Thampatty, 2008). The evident phenomenon of cell mechanotransduction is not clearly understood, but it is believed that the mechanical stimuli applied to the ECM are transmitted inside the cell via integrin-mediated cell adhesion (Juliano and Haskill, 1993; Maniotis *et al.*, 1997). Integrins are transmembrane receptors with two domains, the ECM and the cytoplasmic domain, that mediate interactions between the cytoskeleton and ECM and are primarily responsible for the mechanotransduction process. Therefore, integrins, ECM, and cytoskeleton are significant players in the study of cell mechanics (Hynes, 1992; Ingber, 1991, 1993). The "tensegrity model" helps to understand the cell mechanics when a mechanical force is initially applied to the plasma membrane and immediately imparted to the cell nucleus via inter-associated cytoskeleton networks and causes activation of several gene expressions (Ingber, 1993; Wang *et al.*, 1993).

In addition to the cytoskeleton and integrins, G proteins are also essential members of mechanobiology. To understand the effect of mechanical stress on G-protein coupled receptors (GPCR), bradykinin B2 (B2K) receptors displayed by bovine aortic endothelial cells are first labeled fluorescently with a yellow fluorescent protein (YFP) and cyan fluorescent proteins (CFP) and subjected to shear stress of ~30 dynes cm^2 (for 2 min), leading to observable spectral changes (Fig. 2b(i)). As illustrated in Fig. 2b(ii), the fluorescence decay kinetics of cyan fluorescent protein and yellow fluorescent protein indicates that shear stress causes conformational alterations in the GPCR (Chachisvilis *et al.*, 2006). The concentration of Ca^{2+} inside the cell also plays a vital role in cell mechanics. Fibroblast cells (NIH3T3) labeled with Fluo-4 were used to examine the effect of stretching forces on cells. The stretching force applied to the fibroblast cells results in an enhanced intensity of the Fluo-4 (Figs. 2c(i) and 2c(ii)), that is proportional to the concentration of intracellular Ca^{2+}; suggesting that applying force to the cells also impacts the calcium concentration inside the cell, which further regulates cellular functions (Munevar *et al.*, 2004).

Influence of mechanical cues on cell adhesion

Membrane deformation leads to membrane adhesion and the activation of G proteins that initiate various cellular events (Gudi *et al.*, 1998; Gudi *et al.*, 1998). The activity of phosphoinositide 3-kinase attributes to the membrane geometry (Hübner *et al.*, 1998). The glycosylphosphatidylinositol (GPI)–anchored proteins potentially function in sensing the mechanical stimuli, as it has been demonstrated that the GPI-linked urokinase plasminogen receptors transduce stresses to the cytoskeleton from the cell surface (Wang *et al.*, 1995). The urokinase plasminogen receptors are physically associated with β-1 integrin to transmit mechanical signals (Wei *et al.*, 1996). Cells are attached to the ECM scaffolds through various receptors called focal adhesion (FA) complexes and to the nearby cells through the junctional complexes. FA complexes include integrins and a range of cytoskeleton-linked proteins (such as vinculin, talin, α-actinin, focal adhesion kinase, and paxillin), which link the F-actin to the integrin's cytoplasmic tail. These components link and physically connect the ECM to the cytoskeleton (Burridge *et al.*, 1988). As illustrated in Fig. 3a, it is widely acknowledged that integrin, which regulates cell-ECM attachment, can transfer mechanical signals through the membrane. For instance, mechanical forces applied by integrins caused synchronized changes in nuclear and cytoskeleton structure, demonstrating a long-distance force-transferring roadmap from receptor proteins to the nucleus (Maniotis *et al.*, 1997). Blocking the interaction between integrin-ECM inhibits the effect of mechanical forces on the cells (MacKenna *et al.*, 1998; Muller *et al.*, 1997; Salter *et al.*, 1997; Wilson *et al.*, 1995). It is clear from the studies that integrins, which represent a class of transmembrane receptors, are a potential candidate for transferring mechanical stimuli and transmitting instructions encoded in these stimuli into biochemical signals, leading to biological reactions. Platelet-endothelial cell adhesion molecules (PECAM), E-cadherin, and E-selectin are the other adhesion molecules that potentially transfer force through the cell surface to the cytoskeleton (Potard *et al.*, 1997; Wang and Ingber, 1995; Yoshida *et al.*, 1996). The crucial features of cell mechanobiology and its importance in disease and physiology have created tremendous interest in developing techniques for assessing the mechanical characteristics of cells. Cells transmit extracellular or intracellular forces through localized sites at which they adhere to other cells or an extracellular matrix. Various methods have been proposed to examine cell adhesion events by analyzing single cells and cell populations. In general, studies on cell adhesion are grouped into cell attachment and detachment events. Cell adhesion attachment processes rely on the mechanics of cell attachment to the substrate, whereas cell detachment events include applying load to separate the attached cells from the substrate. The examination of the cell adhesion events can be grouped into single cell and cell population analysis (Ahmad Khalili and Ahmad, 2015). The ECM is composed of many proteins and other materials that are required for cellular interactions as listed in Table 1.

Scaffolds-assisted mechanotransduction

Scaffolds offer the needed support for cell growth and attachment in a 3D milieu, resulting in the development and self-assembly of engineered tissue. The mechanical impact of the scaffolds depends on the designed architecture and characteristics of the scaffold, which include pore size and shape, materials, biodegradability, and elasticity. Scaffolds with varying properties affect cells' nature and activity (Dado and Levenberg, 2009). The *in vivo* conditions and the functions of the ECM surrounding enclosed cells can be recreated in a 3D culture system with an extent of

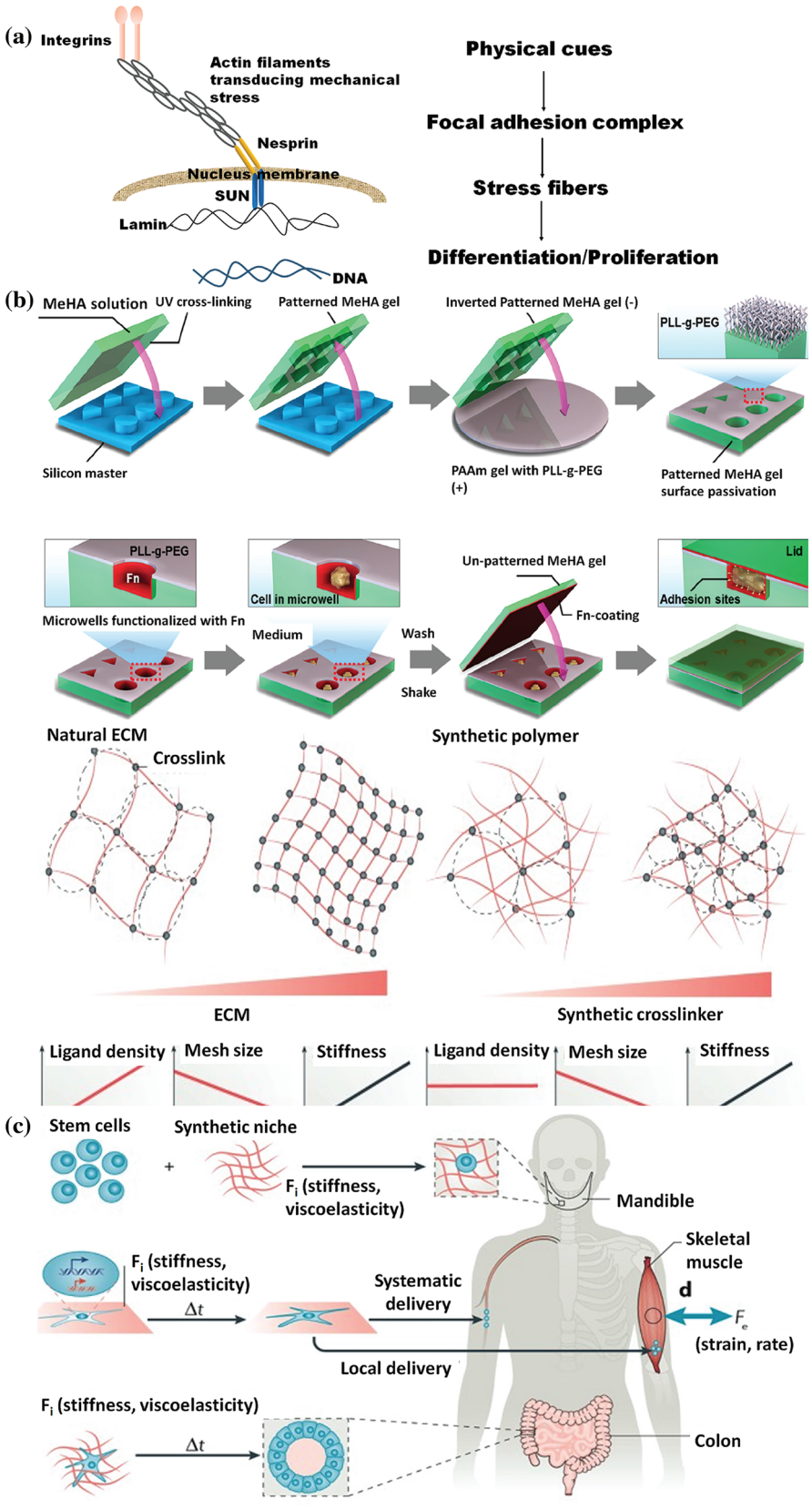

FIGURE 3. (a) A schematic representation of the interaction between the nucleus and cytoskeleton (Patten and Wang, 2021); (b) Designing and Synthesis of scaffolds with different geometry (Bao *et al.*, 2018b); (c) Utilization of stem cell mechanobiology for tissue engineering applications (Vining and Mooney, 2017).

complexity that allows cells to behave similarly to their native environment (Naqvi and McNamara, 2020).

Scaffold stiffness

To generate the mechanotransduction phenomenon, cells examine substrate stiffness and other environmental stimuli and respond through biochemical components such as the cytoskeleton (Ingber, 2006). There is an interrelationship between the matrix stiffness and cell behavior; the collagen-coated gel of polyacrylamide of stiffness comparable to muscle tissue results in enhanced striations of myotubular actin/myosin (Engler *et al.*, 2004). The stiffness of the

TABLE 1

Major components involved in cell-ECM interplay and their response to mechanical stimulus

Component	Location	Function	Mechanical force/stress-associated cellular events	Literature references
Integrins	Cell membrane	ECM-Cytoskeleton interaction, cell motility, cytoskeleton organization	Activation of integrins leads to the activation of FAK (focal adhesion kinase)/c-Src, Cav-1/Fyn signaling	(Giancotti and Ruoslahti, 1999; Schoenwaelder and Burridge, 1999; Shyy and Chien, 2002)
Focal adhesions	The transmembrane core of α and β integrin	Facilitates force transfer between cells and ECM	The enhanced kinase activity of FAK	(Burridge *et al.*, 1988; Li *et al.*, 1997; Lo, 2006; Romani *et al.*, 2021)
Fibronectin	Body fluids (soluble form), ECM (insoluble form)	Formation of stress fibers	Normal fibroblast activation (NAF)/ Cancer-associated fibroblast (CAF) genesis	(Potts and Campbell, 1994)
Kindlins	Ectodermal cells	Regulate integrin signaling and cell-matrix interactions	Upregulation of Kindlin-2 and downregulation of Smad2/3 and Sclerostin	(He *et al.*, 2011; Plow and Qin, 2019; Qin *et al.*, 2021)
Collagen	Cell membrane basement	Cell recruitment provides tensile strength	Stimulation of collagen transcription factors	(Fleck and Simman, 2010; Jin *et al.*, 2003)
Cytoskeleton	Plasma membrane	Defines membrane topology, interaction with internal organelles	Activation of Rac and Rho GTPase and induction of actin cytoskeleton reorganization	(Birchmeier, 1984; Birukov *et al.*, 2002; Bretscher, 1991)
Talin	Cell junction	Integrin activation promotes connections of integrins to the actin cytoskeleton	Conformational alteration in talin exposes binding sites for vinculin	(Ciobanasu *et al.*, 2014; Haining *et al.*, 2016; Klapholz *et al.*, 2015; Yan *et al.*, 2015)
Proteoglycans	Pericellular matrix, cell membrane	Activation of metalloproteinases	Enhanced chondroitin sulfate proteoglycan	(Caterson and Lowther, 1978; Iozzo and Schaefer, 2015)
ROCK (Rho-associated kinase)	Chromosomes	Stress fiber formation, actin organization	Upregulation of caveolin-1/ROCK signaling with enhanced proliferation	(Dohi *et al.*, 2019; Julian and Olson, 2014; Liao *et al.*, 2007)

matrix has also been shown to control cell differentiation; for example, mesenchymal stem cells, when cultured on polyacrylamide gel with rigidities similar to that of bone, brain, and muscle tissues, caused the cells to differentiate into osteoblasts, neurons, and myoblasts respectively (Engler *et al.*, 2006). Furthermore, it has been demonstrated that the compliance of the substrate may also affect the interactions between nearby endothelial cells. A gentle or soft substrate promotes continuous interactions, whereas a rigid substrate triggers migratory behaviors (Reinhart-King *et al.*, 2008). In a 3D system, the influence of matrix stiffness on stem cell behavior was examined by encapsulating mesenchymal stem cells in poly (ethylene glycol) dimethacrylate of different weight percentages, with which acryloyl-PEG-GRGDS2 was then crosslinked. The cells enclosed in a moderately stiff (11–30 kPa) hydrogel scaffold favored osteogenic differentiation, while the scaffold stiffness of (2.5–5) kPa was preferred for adipogenic differentiation (Huebsch *et al.*, 2010).

Additionally, the mechanical characteristics of PLGA/PLLA scaffolds affect skeletal muscle cell differentiation, organization, and viability; during culture time, stiff scaffolds encourage the differentiation of cells to produce myotubes (Levy-Mishali *et al.*, 2009). Adipogenic differentiation of mesenchymal stem cells (MSCs) occurs when they are enclosed in chemically crosslinked non-degradable hyaluronic acid (HA) stiffness matrices ranging from 4.4–91 kPa, while the degradable HA matrices lead to the osteogenic differentiation of MSCs (Khetan *et al.*, 2013). It is suggested that the differentiation of MSCs can be mediated via the cues offered by crosslinking the hydrogel. Given that scaffold stiffness significantly impacts cell function and tissue integrity, various techniques have been devised to manage scaffold stiffness effectively (Fig. 3c). The range of methods involves adjusting the scaffold's chemical composition, applying a specified strain, adjusting the architecture, and employing different crosslinking procedures (Cornwell *et al.*, 2007; Hadjipanayi *et al.*, 2009; Karamichos *et al.*, 2007; Lee *et al.*, 2001; Levy-Mishali *et al.*, 2009; Nirmalanandhan *et al.*, 2008). In addition to traditional scaffold manufacturing methods, cell culturing parameters may also modify the stiffness of scaffolds; matrix synthesis and cell-derived molecules produced after culturing are responsible for these findings (Karamichos *et al.*, 2006).

Scaffold geometry

Pores of various sizes and geometries, like rectangles, squares, and cylinders, can alter the function of a cell's

mechanotransduction machinery (Han *et al.*, 2022). Cells can be seeded or injected into a scaffold's pore structure for delivery to the damaged site. Once inside the pores, the cells adhere to the scaffold surface and subsequently differentiate, proliferate, migrate, and release ECM constituents to aid tissue remodeling (Han *et al.*, 2022). The scaffold's geometry regulates the matrix by applying a mechanical force gradient to the cells to alter their behavior (Chen *et al.*, 1997). Thus, the ability to recognize geometric properties from meso-to-microscale exists in cells cultured on the surface of the scaffolds (Bao *et al.*, 2018a). For instance, when C2C12 cell lines (myoblast cells) were seeded on fibronectin polydimethylsiloxane with square and rectangular micropatterns, the square geometry showed an increased distribution of histone lysine methyltransferase (SMYD3) compared to the rectangular geometry (Pereira *et al.*, 2020). It has also been demonstrated that the extracellular-related kinase (ERK ½), c-jun N-terminal kinase (JNK), and wingless-type (Wnt) signaling can switch MSCs' differentiation between adipocytes (round) and osteoblasts (triangle) in a geometry-dependent approach (Kilian *et al.*, 2010). Notably, it is noted that 3D microwells of methacrylate hyaluronic acid (at different volumes of 2800, 3600, and 600 μm^3) with triangle, circle, square, and rectangle geometry revealed that among them, only the triangle-shaped microwell enabled cell proliferation and the presence of F-actin and β1 integrin was also observed on both sides of the well (Fig. 3b) (Bao *et al.*, 2018b). In another study, methacrylate hyaluronic acid hydrogel was utilized to create a porous substrate with various geometries (triangular, cuboid, cylinder, and cube) when human-derived mesenchymal stem cells (hBMSCs) were cultured on them instead of cubic and cylinder pores, the cuboid and triangular pores displayed an increased YAP/TAZ nuclear localization (Bao *et al.*, 2017).

Distinctive tissues possess a diverse arrangement of a 3D network of ECM fibrils, for example, isotropic fibers in kidneys and aligned fibers in the tendons (Theocharis *et al.*, 2019; Wang *et al.*, 2018b). As a result, ECM's 2D and 3D organization can be regulated by biomaterials with varied geometry. Wang *et al.* (2018b) revealed that an enhanced alignment of ECM on 2D surfaces caused cells to acquire an extended uniaxial shape with enhanced migration and increased Rac activity in fibroblast cells. Consequently, the geometry of a scaffold can be manipulated to regulate the ECM organization and cell migration through a mechanotransduction process (Han *et al.*, 2022). Understanding the critical influence of scaffold geometry on matrix-assisted cellular activity results in developing strategies for manufacturing 3D scaffolds with predetermined geometry (Dado and Levenberg, 2009).

Scaffold anisotropy

The anisotropy of a material is the characteristic that enables the material to possess different properties when measured in different directions. The successful induction of coordinated cellular proliferation and migration by scaffolds possessing anisotropic macrostructures can promote tissue regeneration (Li *et al.*, 2019; Wang *et al.*, 2020a). Mechanical stretching, ion diffusion, molding, and unidirectional freezing help create scaffolds for various tissue regeneration (Yao *et al.*, 2010; Zhu *et al.*, 2019). Anisotropic scaffolds with directed channels or pores offer cells guiding cues that alter the rate and direction of their growth. According to the research, these structures are beneficial for spinal cord injuries because they encourage orientation, myelination, and outgrowth of axonal and glial cells (Echave *et al.*, 2019; Huang *et al.*, 2020; Rose *et al.*, 2017; Yao *et al.*, 2018; Yu *et al.*, 2020). Antman-Passig and Shefi (2016) fabricated a 3D anisotropic scaffold by incorporating magnetic nanoparticles (mNPs) into the collagen hydrogel and employing an external magnetic field. The neuron cells cultured on the magnetically activated scaffold exhibited typical behavior with high viability and activity (Antman-Passig and Shefi, 2016). Scaffolds with flexible, hydrophilic characteristics can be coupled with topographical signals from fibers to simulate axons' structure. Aligned fibers allow neurites' extension, and the scaffold safeguards nerve cells inside the 3D framework, which holds promise for bioinspired nerve regeneration. Thus, anisotropic scaffolds with fibrous structures offer a favorable environment for promoting *in vivo* axonal growth (Du *et al.*, 2017; Wang *et al.*, 2019; Wu *et al.*, 2019; Zheng *et al.*, 2021). A self-forming multichannel nerve guide conduit (NGC) was fabricated by Wang *et al.* (2020b) using a shape-memory poly (lactide-co-trimethylene carbonate) polymer. They inserted the NGC into a rat sciatic nerve defect and reported the ability of the conduit to promote nerve regeneration based on the functional evaluation and histological analysis, indicating its ability to repair peripheral nerve abnormalities. Based on these findings, it can be concluded that the anisotropy of a scaffold is an important parameter that enables the unpredictable potential in tissue regeneration (Hu *et al.*, 2022; Zhang *et al.*, 2022).

3D printing methods for scaffolds preparation

Fabrication methods for mimicking the biological activities of cells and tissues include designing a fundamental and structural framework referred to as a scaffold that can support and accommodate the growing cells (Weißenbruch *et al.*, 2022). The most crucial function that scaffolds play is assisting and directing the growth of cells and tissues; in some cases, it also serves as a vehicle for the administration of bioactive chemicals (Hatamzadeh *et al.*, 2016a; Hatamzadeh *et al.*, 2016b). They promote adhesion, migration, and proliferation of the cells, which eventually result in the creation of new tissues; they also influence the characteristics of material transport across the tissues (Tenje *et al.*, 2020). The potential to induce a specific cellular response for the regeneration of new tissues is determined by the designed scaffold's biological, mechanical, and physiochemical properties (Achberger *et al.*, 2019; Lemma *et al.*, 2019; Spiegel *et al.*, 2020). The two main aspects of fabricating the tissue repairment porous scaffolds are creating interconnected porous structures and maintaining the proper scaffold shape and size (Duan *et al.*, 2014; Pan *et al.*, 2015). Various 3D printing techniques, such as stereolithography, electrospinning (Fig. 5a), and extrusion-based printing, including direct ink writing and fused

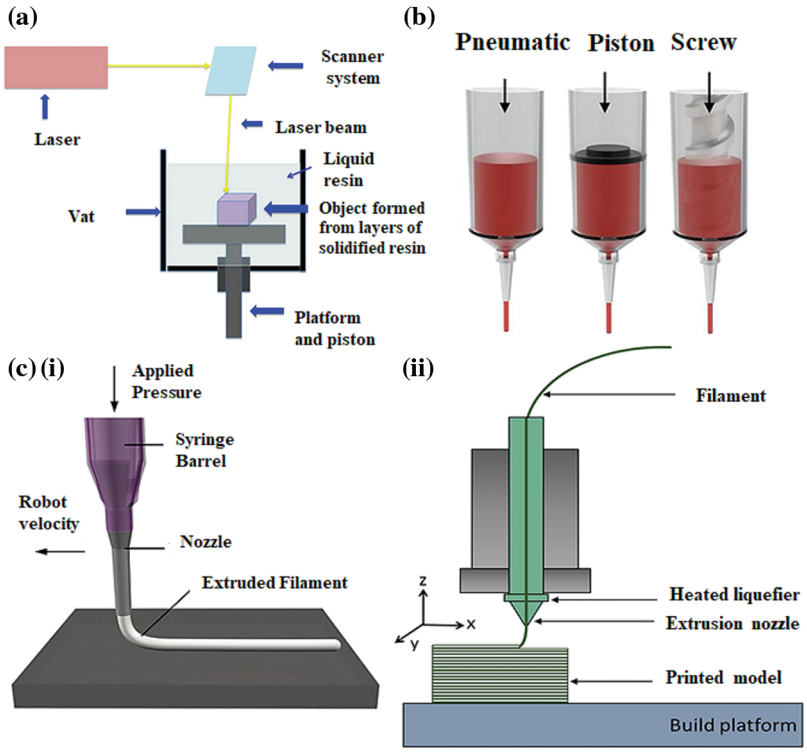

FIGURE 4. 3D printing technologies for the development of scaffolds (a) a stereolithography (SLA) printer (Konta *et al.*, 2017); (b) main components of an extrusion-based 3D printer (Jeong *et al.*, 2020); (c) (i) direct ink writing (DIW) printer (Wan *et al.*, 2020); (c) (ii) fused deposition modeling (FDM) printer (Shanmugam *et al.*, 2021).

deposition modeling, allow the synthesis of scaffolds and perform a vital role in tissue regeneration. Some of the printing methods are discussed in the following subsections.

Stereolithography (SLA)

The first additive manufacturing technique to be established and widely used is stereolithography (SLA). The polymerization of bioinks in a 2D layer is controlled using stereolithography rasters that employ a laser beam (Fig. 4a). A UV or visible light source is used to cure a photosensitive hydrogel of polymers such as alginate, hyaluronic acid, and poly (ethylene) glycol (Wang *et al.*, 2021). The process of curing occurs after the deposition of each layer of a substance. When a layer is polymerized, the procedure is rehashed, adding one layer over the previous layer until the whole scaffold is built. A photoinitiator in the liquid polymer resin allows the production of free radicals after absorbing light of a specific wavelength and enables the initiation of polymerization. The production of high-resolution structures is made possible by adjusting several polymerization method parameters, including printing speed, layer thickness, light energy and intensity, and exposure duration (Chen *et al.*, 2018; Hong *et al.*, 2005; Lovell *et al.*, 2001; Watters and Bernhardt, 2018; Yankov and Nikolova, 2017; Zhang *et al.*, 2019).

The SLA technique makes printing various composites possible if the composite possesses a photopolymerizable material or is chemically altered to be used for bone tissue engineering scaffolds (Huang *et al.*, 2017). This technique offers several advantages, such as fast printing speed, high accuracy, smooth surface finish, and high quality. The general printing precision of a typical SLA printer occurs between 1.2–200 μm, depending upon the layer thickness and laser diameter (Ali *et al.*, 2014; Sears *et al.*, 2016). The technique utilizes biomaterials such as composites, ceramics, and biopolymers; composites used in 3D printing methods improve the performance of scaffolds. Lee *et al.*, 2011 used the micro-stereolithography technique to develop a bone-specific poly (propylene fumarate)/diethyl fumarate scaffold and incorporated it with the bone morphogenic protein-2 (BMP-2) loaded microspheres for rat cranial bone. The *in vivo* results showed enhanced bone formation due to the release of BMP-2 from the scaffold (Lee *et al.*, 2011). Hence, the technology is promising in developing tissue engineering applications structures.

Extrusion-based 3D printing

The extrusion-based 3D printing technique was first developed by Crump (1992). This technique is rapidly emerging in the biomedical field. The method employs a broad spectrum of fluids with viscosities varying from 29 mPa s^{-1} to 6 × 10^7 mPa s^{-1} (Ahmad *et al.*, 2019; Crump, 1992). The technique uses a screw device or pneumatic actuator (Fig. 4b) to feed substances via a cartridge or a nozzle for layer-by-layer material deposition. This method allows a high affinity with many materials and attributes a curing step such as light activation or chemical curing. The layer-by-layer deposition of the material can be regulated by actuators that control the arrangement of the nozzle in 3D. Manufacturing complex structures with this technique necessitates a supporting platform as each layer is built above the other (Placone and Engler, 2018). Conventionally, the extrusion method extrudes material by applying pressure. For the printing of tissue-specific scaffolds, the melted polymeric ink is ejected from the nozzle under gradual pressure; the 3D-printed scaffold is generated under the mutual action of the nozzle and lifting table (Duan *et al.*, 2014). To design complex 3D

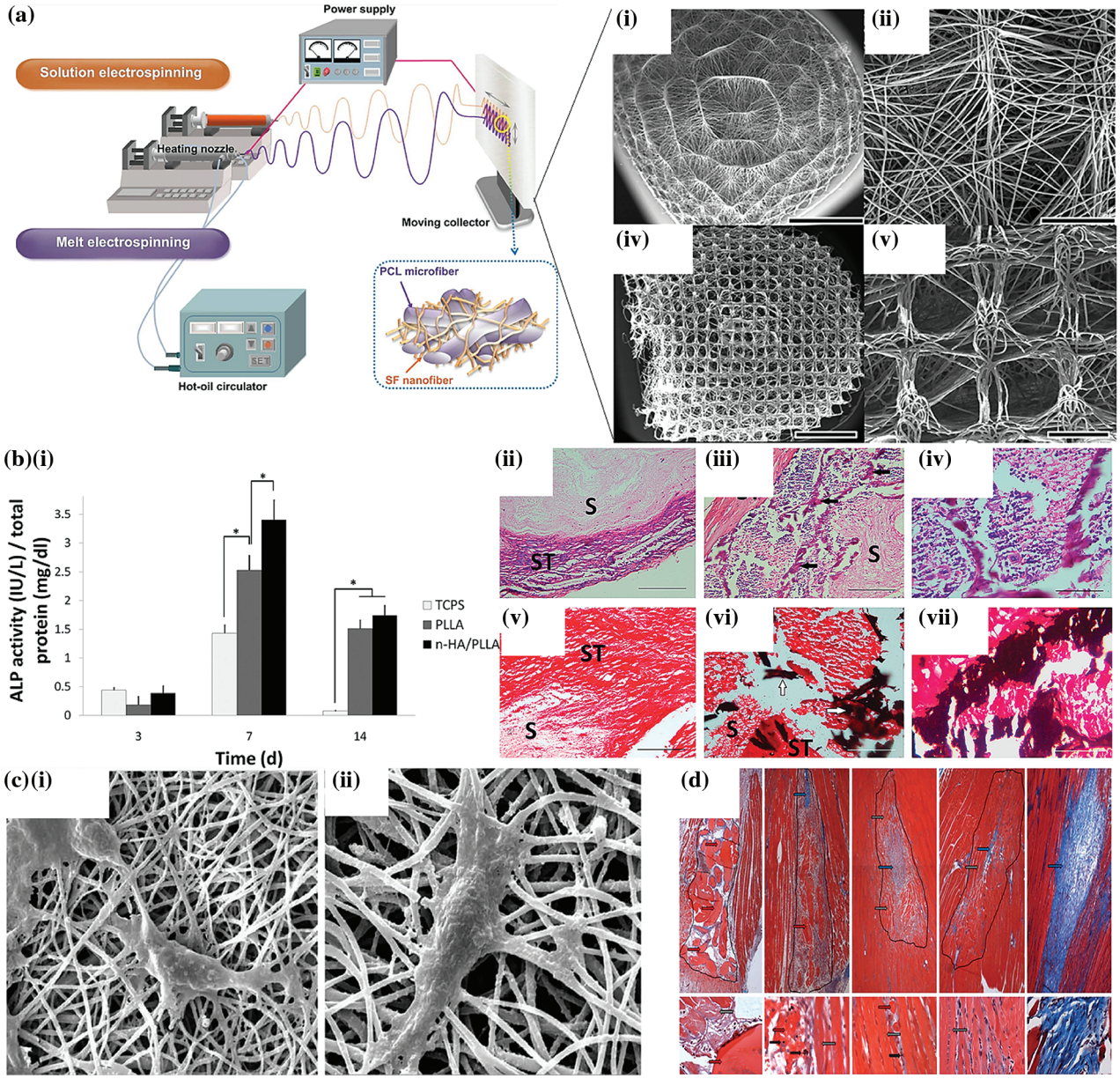

FIGURE 5. (a) Electrospinning system fabricating micro/nanofibrous scaffold (Jun *et al.*, 2018; Kim *et al.*, 2015a); (b) (i) alkaline phosphatase activity of the cultured stem cells on different scaffolds, (ii–iv) HE staining (v–vi) Von Kossa staining images for the bone formation and calcium deposition analysis (Seyedjafari *et al.*, 2010); (c) SEM images of the chondrocyte proliferation on PHB-chitosan-MWCNT scaffolds (i & ii) day 3 and day 7 (Mohammadalizadeh *et al.*, 2020); (d) muscle wound morphological characteristics followed by 2, 7, 14, and 70 days after transplanting cell loaded fibrin thread based implant (Page *et al.*, 2011).

objects, CAD (computer-aided design) software is used to optimize the design. Depending upon the printing temperature, extrusion-based 3D printing methods are divided into two main types: (a) Direct ink writing and (b) Fused deposition modeling (Karyappa and Hashimoto, 2019).

Direct ink writing (DIW)

Direct ink writing (DIW) is an extrusion-based 3D printing technique that allows the manufacturing of objects with intricate geometry. In this process, a viscoelastic ink (fluid) is extruded from a printing nozzle to form scaffolds or fibers at room temperature (Fig. 4c(i)), which further accumulates to form a particular pattern as the nozzle moves (Karakurt and Lin, 2020; Li *et al.*, 2021); because of gravity's influence, the ink is preferentially deposited after wetting the surface. Following a rapid decrease in stress, solvent evaporation, phase change, polymerization, or due to a combined effect, the ink solidifies and builds a structure with the desired properties. DIW is further recognized as Robocasting and is typically classified into two distinct types: droplet and continuous ink extrusion (Lewis *et al.*, 2006; Saadi *et al.*, 2022). The cost-effectiveness and potential to combine various materials in a single-step process in this technique have garnered the attention of many research institutes, and researchers employ DIW constructs for drug encapsulation, soft robotics, and developing touch sensors (Haque *et al.*, 2018; Karakurt and Lin, 2020; Saadi *et al.*, 2022). DIW offers a variety of applications in various areas by monitoring the viscoelastic ink (Karakurt and Lin, 2020).

Fused deposition modeling (FDM)

Fused deposition modeling (FDM) creates 3D structures by using continuous thermoplastic polymer filaments. The main components of a fused deposition modeling setup are a material feed, a gantry, a liquefier print head, and a building surface (Parandoush and Lin, 2017). The operation of FDM can be illustrated by extrusion method, in which the raw material or fed stock is supplied in the form of continuous strips that flow between rollers and get liquified within the liquefier at a temperature higher than its melting point (Dudek, 2013; Varma *et al.*, 2020). The semi-liquid molten filaments are extruded via a nozzle and successively deposited in thin layers on the platform aligned to the XY plane. After the layer deposition, the nozzle head or platform moves along the Z-axis to accurately follow single-layer thickness for subsequent layer assembling (Mandala *et al.*, 2022; Vyavahare *et al.*, 2019). The complete 3D object is produced after a certain period and does not require further processing (Dudek, 2013). This technology, generally with thermoplastics employed as the feed material, generates extremely durable objects in a straightforward one-step procedure appropriate for practical use and provides complete flexibility (Ian Gibson, 2015; Novakova-Marcincinova and Novak-Marcincin, 2012). Fig. 4c(ii) shows the main components of an FDM printer used for creating 3D scaffolds.

Biomimetic scaffolds and tissue engineering

In tissue engineering and regenerative medicines, in addition to the administration of cells to the damaged site by encapsulating them within a scaffold, cells can also be injected or seeded directly inside the pore structure of the scaffold, where the cells attach to the surface of the scaffold and eventually continues the proliferation, differentiation, and secretion of ECM factors to aid in the remodeling and regeneration of the damaged tissues. Therefore, the cells seeded on scaffold surfaces can detect the surface's geometric properties and translate these cues into mechanical stresses that result in nuclear deformation and changes in gene expression (Bao *et al.*, 2018a; Callens *et al.*, 2020).

Numerous strategies attempt to harness the potential of biomimetic scaffolds to sustain and direct adult stem cell differentiation. The differentiation of mesenchymal stem cells into adipose or osteogenic precursor cells is a mechanosensitive process influenced by the substrate's stiffness and topography. The bioinspired scaffolds that enhance osteogenic cell differentiation are the fibrous meshwork scaffolds (Figs. 5a(i)–5a(iv)) that can be produced from synthetic material or obtained from biological sources. The biological materials include aligned and decellularized ECM and chitosan/collagen-derived nanofibers; however, polycaprolactone and polyethylene glycol are synthetic materials used to fabricate scaffolds (Abdelmoneim *et al.*, 2020; Azoidis *et al.*, 2017; Ventre *et al.*, 2019; Xie *et al.*, 2016). Table 2 is a list of biomaterials and the effects of exerted mechanical response on different cell types. Furthermore, to improve the rheological properties and enhance the synthesis of mineralized bone matrix, various organic and inorganic components can be effectively incorporated into the scaffold's backbone (Abdelmoneim *et al.*, 2020; Persson *et al.*, 2018). Recent research developed a highly porous, collagen-functionalized scaffold by employing poly (3,4-ethylene dioxythiophene) polystyrene sulfonate (PEDOT: PSS) as a conductive material. The study revealed that the designed scaffold facilitates osteogenic development and can be a potential candidate for bone tissue regeneration (Iandolo *et al.*, 2020). Electrospun fiber scaffolds comprised of silk fibroin, hyaluronic acid, or polyacrylamide can initiate neurite expansion; their functionalization supports the particular fate of neuronal cells (Farrukh *et al.*, 2017; Hamsici *et al.*, 2017; Seidlits *et al.*, 2019; Sun *et al.*, 2017; Wu *et al.*, 2017). The incorporation of conductive materials such as polyethylene glycol (PEG), poly (3,4-ethylene dioxythiophene), polypyrrole hybrid polymers, and graphene for electrical conduction in the scaffolds leads to the upregulation of glial and neuronal marker proteins (Feig *et al.*, 2021; Rose *et al.*, 2017; Tomaskovic-Crook *et al.*, 2020, 2019; Wang *et al.*, 2018a). Neuronal progenitor cells exhibit a preferential differentiation into the neurons when plated on the scaffolds modified with the laminin-derived peptide sequence (IKVAV) (Silva *et al.*, 2004).

Cartilage regeneration

The most frequent health illnesses are driven by trauma, congenital disease, and aging, the most prevalent cause of cartilage abnormalities. Due to its avascular, lymphatic, and aneural structure, insufficient availability of chondrocytes impedes and obstructs the recovery process at the cartilage defect site. Various types of scaffolds can be manufactured for the regeneration of cartilage tissues based on the availability of polymers and printing methods (Nikbakht *et al.*, 2020). Nanofibrous scaffolds have garnered considerable attention because of their remarkable qualities, including the ability to accommodate labile biomolecules, high volume-to-surface ratio, similarity to the ECM of native tissue, and tunable physical and chemical properties (Farzamfar *et al.*, 2018; Khoshnevisan *et al.*, 2018). Typically, various materials can be used to meet the requirements of an effective scaffold for cartilage tissue regeneration. The blend of synthetic and natural polymers strengthens the physical and mechanical properties of the scaffolds, respectively (Jaymand *et al.*, 2016). Poly (3-hydroxybutyrate) is among the most examined poly-hydroxyalkonate, which is biologically compatible with various cells, but its low hydrophilicity and degradation rate need to be improved for their use in cartilage tissue engineering (Cai *et al.*, 2016). Mohammadalizadeh *et al.* (2020) developed a multi-walled carbon nanotube (MWNTs) nanofibrous scaffold dispersed in PHB-chitosan that exhibited increased hydrophilicity and three times greater tensile strength. When the chondrocytes were cultured, the scaffolds demonstrated improved growth and cell adhesion properties along with mechanical features similar to the human articular cartilage. 1% MWNTs/PHB-chitosan nanofibrous scaffolds were reported to be the most effective and successful for cartilage tissue regeneration in terms of the structural and biological aspects (Figs. 5c(i) and 5c(ii)) (Mohammadalizadeh *et al.*, 2020). The high mechanical strength and electrical conductivity of the

TABLE 2

Biomaterial-stimulated mechanical response and effects on different cell types

Biomaterials	Cell type	Fabrication technique	Mechanical response	Effects	Refs.
Polyvinylidene fluoride (PVDF), Barium titanate (BTO), Multiwall carbon nanotubes (MWCNT)	PC12, S42, hNSCs	Electrospinning	YAP nuclear localization, enhanced Ca^{2+} influx	An outgrowth of neurites and neural cell proliferation	(Hoop *et al.*, 2017; Kim *et al.*, 2020; Lee and Arinzeh, 2012)
Poly (ester amide) graft amino-capped tetra-aniline (PEA-g-TA)	MC3T3-E1	–	Enhanced ALP enzyme activity and Ca^{2+} concentration	Improved osteoinductivity	(Cui *et al.*, 2012; Hardy *et al.*, 2013; Hemmrich *et al.*, 2008; Jokhadze *et al.*, 2007)
Poly (lactic-co-glycolic acid (PLGA),	C2C12	Soft-lithography, melt-casting	Activation of FAK and MAPK signaling	Increased myogenic differentiation	(Gao *et al.*, 2021; Park *et al.*, 2005; Xu *et al.*, 2014)
Polycaprolactone (PCL)	hOBs	Melt electrowriting	Reduced nuclear YAP localization in the 3D substrate	Enhanced expression of osteogenic marker genes	(Fazeli *et al.*, 2021; Han *et al.*, 2022; Han *et al.*, 2021)
Porous metallic scaffold	MC3T3-E1	Laser cutting	YAP nuclear translocation	Improved osteogenesis and angiogenesis	(Kelly *et al.*, 2021; Liu *et al.*, 2022b)
Poly (ether carbonate urethane) urea (PECUU), Decellularized annulus fibrosus matrix (DAFM)	AFSCs	Electrospinning	Increased YAP localization in the substrate with high stiffness	Maturation of annulus fibrosus	(Chu *et al.*, 2019; Liu *et al.*, 2022a; Zhu *et al.*, 2016)
Poly (L-lactic acid (PLLA)	hASCs	Electrospinning	Increased YAP/TAZ localization	Secretion of immunomodulatory factors	(McCullen *et al.*, 2009; Wan *et al.*, 2018)

MWNTs make them an adaptive candidate for application in cartilage tissue engineering (Mohammadalizadeh *et al.*, 2020).

Bone regeneration

Bone injuries and defects pose a serial clinical issue. The risk of musculoskeletal diseases like scoliosis, fracture, osteoporosis, or tumors and diseases like osteoarthritis is rapidly increasing due to the aging global population and longer life expectancy (Agarwal and García, 2015; Roseti *et al.*, 2017). Symptoms like mal-union are frequent seen in patients with severe injuries and restrict the bone from complete recovery (Holzwarth and Ma, 2011). The traditional methods for bone repairment, including bone grafting, hold many limitations due to the lack of availability of donors and the risk of immune rejection. Therefore, the emerging field of tissue engineering offers a novel solution for bone regeneration by developing a potential polymeric scaffold combined with cell and growth factors. The scaffolds are constructed to recreate the natural ECM's nanofibrous architecture (Zhang and Ma, 2000). Polymers such as poly-l-lactic acid (PLLA), polycaprolactone (PCL), and hydroxyapatite (HA) are employed for designing the scaffolds and are proven to be effective for the treatment of damaged bone tissues. Seyedjafari *et al.* (2010) developed a hydroxyapatite electrospun PLLA fibrous scaffold seeded with umbilical cord blood (UCB) derived stem cells and inserted into the mice. Following 10 days after the implantation, the results indicated a considerable amount of mineralization with little or no immune reaction to the defective area. The graph in Fig. 5b(i) indicates enhanced mineralization on different scaffolds while Figs. 5b(ii)–5b(vii) shows histological evidence of the bone growth through HE and von Kossa staining (Seyedjafari *et al.*, 2010). Since miRNA can express or suppress the expression of particular genes, it can be employed for tissue regeneration (Peng *et al.*, 2015). Lei *et al.* (2019) manufactured an injectable hydrogel containing miR-222, aspirin, and silica nanoparticles. After injecting the hydrogel into a bone-defected rat, they revealed that the presence of miR-222 in the hydrogel stimulates neural development in mesenchymal stem cells, facilitating bone restoration and neuron formation (Lei *et al.*, 2019). During the bone repair the effect of miR-26a in enhancing osteoblastic activity can be regulated by targeting Gsk-3 (Glycogen synthase kinase 3) during bone repair (Hao *et al.*, 2017). Besides miRNA and ions, it is ideally possible to enhance the functions of scaffolds by utilizing various biological factors such as fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and transforming growth factors (TGF-β) in order to enhance osteogenesis (Wang *et al.*, 2018c). The most extensively researched factor is bone morphogenetic protein 2 (BMP-2), which can be incorporated into the ECM to establish an osteogenic environment and aid bone formation (Kim *et al.*, 2015b).

Muscle regeneration

With more than 50% of body weight made up of muscle tissue, which regulates the body's normal functioning, muscles play a

crucial role within the body. Nevertheless, as muscles possess a delicate structure, injuries are relatively common. Organ damage and difficulty in movement result from muscular damage (Brack and Rando, 2012; Kwee and Mooney, 2017). A clinical procedure such as surgical restoration is often utilized to treat muscular damage. Consequently, its implementation is severely constrained by low survivability (Garg *et al.*, 2015; Klinkenberg *et al.*, 2013). Integrating biomaterials with a cell-based approach can enhance the therapeutic benefits of cells during muscle regeneration. The fundamental goal of a material is to imitate the original environment and, by associating with the cells, establish a microenvironment that allows the tissues to grow. Page *et al.* (2011) produced a fibrin fibers scaffold via the micro-thread extrusion method and cultured it with the muscle cells before implanting the scaffold in a significant muscle lesion in the anterior tibialis of mice. The transplanted cell-loaded scaffold promoted the formation of muscle fibers and dramatically lowered fibrosis-related protein expression at the wound site. Fig. 5d depicts the area with regenerating muscles implanted with micro-thread containing less collagen compared to the untreated group (blue arrow) (Page *et al.*, 2011). Patel *et al.* (2016) constructed a hierarchical carbon scaffold to promote myoblast growth and differentiation. The scaffold was designed in nano and micro-scale geometries. Aligned carbon-fiber mat and random microporous carbon foam were distinct kinds of manufactured scaffolds, and both were grafted with carbon nanotubes to achieve a nanoscale architecture. C2C12 cells exhibited similar proliferative and adhesive properties on both scaffolds. Consequently, the well-aligned fibrous scaffold assists in the conversion of myocytes to myotubes (Patel *et al.*, 2016). In addition, the nanoscale geometry (random or aligned) may alter the surface attributes of the scaffold, hence influencing the adherence and proliferation of myoblasts. However, for myotube production, the synergy between architecture and nanoscale is essential (Dong *et al.*, 2020; Patel *et al.*, 2016).

Conclusions and Future Prospects

The remarks of this review point to the expectation of opening and enabling a new avenue of tissue engineering through mechanotherapy induced by innovative biomaterial platforms. Cells receive a range of mechanical cues from the surrounding environment, and these mechanical signals are widely known for modulating cell physiology and the synthesis of various ECM constituents. Understanding the interaction between cells and matrix sheds light on the development of structures that can mimic the natural environment of ECM and can be a potential parameter for regenerating damaged tissues and organs. Factors including substrate stiffness and architecture are crucial to the study of mechanobiology. Designing scaffolds by regulating the stiffness and surface chemistry helps support cells and tissues' growth and development. These strategies are essential in investigating and studying cell mechanics that provide a blueprint for developing smart materials in the biomedical field. Despite the versatility and properties offered by 3D scaffolds to simulate cellular microenvironments, several challenges and limitations hinder their application in tissue engineering. For example, the materials used for synthesizing a tissue-specific construct sometimes reduce cell proliferation and trigger the host immune response after implantation; hence, the development of advanced green biomaterials that show enhanced compatibility with the host's immune system and high degradability needs to be undertaken. The printing resolution of the fabricated scaffold is another challenging parameter; for printing structures with a high resolution, a highly viscous ink is preferable, which damages the cells and restricts their application. Developing a mechanically stable scaffold requires a crosslinking step but, crosslinkers such as glutaraldehyde cause toxicity. Therefore, improved crosslinking methodologies should be applied using crosslinkers such as citric acid and carboxylic acid to strengthen the low mechanical properties. Thus, different types of nature-based polymers and crosslinking agents should be developed to minimize the abovementioned challenges.

Further research is also necessary to analyze the changes in cells and genes during the mechanotransduction process to understand and comprehend the complexity of cell-matrix interplay.

Funding Statement: This research was supported by the Basic Research Program through the National Research Foundation of Korea (NRF), which is financed by the Ministry of Education (Grant Nos. 2018R1A6A1A03025582, 2019R1D1A3A03103828, 2022R1I1A3063302), Korea.

Author Contributions: The authors confirm contribution to the paper as follows: Study conception and design: KTL, AR; Data collection: KTL AR; Data analysis and interpretation: AR, KG, SDD, TVP, DKP; Drafting the article: AR; Critical revision of the article: KTL, SDD; Final approval of the version to be published: KTL.

Availability of Data and Materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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