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Noncoding RNAs and Their Potential Therapeutic Applications in Tissue Engineering

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ABSTRACT

Tissue engineering is a relatively new but rapidly developing field in the medical sciences. Noncoding RNAs (ncRNAs) are functional RNA molecules without a protein-coding function; they can regulate cellular behavior and change the biological milieu of the tissue. The application of ncRNAs in tissue engineering is starting to attract increasing attention as a means of resolving a large number of unmet healthcare needs, although ncRNA-based approaches have not yet entered clinical practice. In-depth research on the regulation and delivery of ncRNAs may improve their application in tissue engineering. The aim of this review is: to outline essential ncRNAs that are related to tissue engineering for the repair and regeneration of nerve, skin, liver, vascular system, and muscle tissue; to discuss their regulation and delivery; and to anticipate their potential therapeutic applications.

1. Introduction

Tissue engineering is a growing area in biomedical research that holds great promise for a range of potential applications in regenerative medicine. It applies the principles of engineering and life sciences in order to develop biological substitutes to repair diseased and injured tissues and organs and restore their functions. The essential characteristic of tissue engineering is the use—whether alone or combined—of living cells, biocompatible materials, biochemical factors (e.g., growth factors, GFs), and physical factors (e.g., cyclic mechanical loading) to create a biomimetic tissue-like structure [1]. The living cells can be derived from donor tissue, albeit with a limited supply; stem or progenitor cells can be used as an alternative cell source [1]. For tissue engineering applications, the cellular microenvironment must allow seed cells to enact their roles, as they do in native tissue, thus ensuring the effective regulation of cell behavior.

Noncoding RNAs (ncRNAs) are a large cluster of RNAs that have multiple functions in diverse cellular processes, although they do not encode proteins. According to their biological functions, ncRNAs can be divided into infrastructural and regulatory types. Infrastructural RNAs include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs), guide RNAs (gRNAs), and telomerase RNAs. Regulatory ncRNAs can be classified into microRNAs (miRNAs), small interfering RNAs (siRNAs), long noncoding RNAs (lncRNAs), Piwi-interacting RNAs (piRNAs), promoter-associated RNAs (PARs), and enhancer RNAs (eRNAs) [2–4].

ncRNAs are considered to be a class of molecular targets that may play an important role in tissue engineering. Approaches for ncRNA-based tissue regeneration therapy include altering endogenous cellular activity using ncRNAs, influencing the behavior of resident stem/progenitor cells or cells incorporated into tissue engineered constructs, or modulating the fate of both implanted and endogenous cells with selected ncRNAs. miRNAs, siRNAs, and lncRNAs are the main regulatory ncRNAs that have current

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potential applications. miRNAs are a class of small ncRNAs that have attracted considerable interest; they can influence a wide range of cell functions, including the control of proliferation, migration, differentiation, apoptosis, and other processes, by down-regulating or up-regulating the expression of their target genes [5–7]. lncRNAs are a major class of eukaryotic transcripts that regulate gene expression, possibly by chromatin remodeling, alternative splicing modulation, interacting with proteins to affect protein activity and localization, or serving as a structural component [8,9]. Moreover, lncRNAs may compete for miRNA binding, thus affecting the regulation and function of miRNA target genes. lncRNAs influence almost every step in the life cycle of genes; their best-studied function occurs in the epigenetic regulation of allelic expression [10,11].

2. The applications of ncRNAs in tissue engineering

The applications of ncRNAs in tissue engineering have received considerable attention. In the following discussion, we outline a variety of ncRNAs that have been used for neural tissue engineering, liver tissue engineering, skin tissue engineering, muscle tissue engineering, and vascular tissue engineering.

2.1. Neural tissue engineering

The nervous system comprises two major components: the central nervous system (CNS) and the peripheral nervous system (PNS). In clinical practice, injuries to the nervous system are commonly encountered. Neural tissue engineering holds great promise for the treatment of diseased or injured nerves, which have a limited capacity to spontaneously regenerate. The poor regenerative capacity of nerve tissues results from the existence of a hostile microenvironment formed by a complex series of events after nerve diseases or injuries. Therefore, an important issue in neural tissue engineering is to manipulate and neutralize the local microenvironment, thus making it more permissive for regeneration.

In neural tissue engineering, the supporting cells that are implanted into the injured nerve may produce GFs or extracellular matrix (ECM) molecules to facilitate nerve regeneration. Neuronal cells and neuroglial cells are the main cell types for neural tissue engineering. Neural stem cells have also been widely used in neural tissue engineering due to their capacity to self-renew and terminally differentiate into mature neural cell types. Therefore, the regulation and potential application of ncRNAs for neural tissue engineering mainly involves neural stem cells, neuronal cells, and neuroglial cells (Table 1) [12–200].

2.1.1. Neural stem cells

Neural stem/progenitor cells (NSPCs): The ability to control the self-renewal and differentiation of transplanted NSPCs is critical for the successful application of neural tissue engineering. miR-25, miR-124/124a, miR-200, and miR-106b-25 clusters can promote the neuronal differentiation of NSPCs, and miR-9 and let-7d can promote the neuronal and astrocytic differentiation of neural stem cells (NSCs) [16,17]. miR-34a can obviously increase the numbers of $NeuN^+$ cells, and can enhance neuronal maturation and the neurite elongation of NSPC-derived neurons. In addition, it is necessary to ensure the subsequent maturation of differentiated cells for proliferation and functionalities. miR-25, miR-137, miR-184, and miR-195 can enhance NSPC proliferation [12–15], which helps provide sufficient cells to restore tissue structure and functionality. miR-137, miR-184, and miR-195 also increase the number of neurons and astrocytes from NSPC differentiation [13–15].

Mesenchymal stem cells (MSCs): MSCs, also called bone-marrow stromal cells, are pluripotent stem cells that come from the stromal compartment of the bone marrow. MSCs are increasingly applied in cell-based therapies for various diseases because they are easily obtained from the bone marrow and can be expanded on a large scale by *in vitro* culture. miR-9 and miR-124 can promote neuronal differentiation of MSCs toward mature functional neurons, while miR-128 negatively regulates the differentiation of MSCs into neuron-like cells [16,21,22].

Table 1
ncRNAs with potential applications for tissue engineering.

Cell type and function	ncRNAs
Nerve	
Neural stem/progenitor cells	
Promote proliferation	miR-25 [12]; miR-137 [13]; miR-184 [14]; miR-195 [15]
Induce differentiation	miR-9, siRNA-TLX [16]; let-7d [17]; miR-137 [13]; miR-184 [14]; miR-195 [15]; miR-34a [18]; lncRNA-BDNF-AS, siRNA-BDNF-AS [19]
Mesenchymal stem cells	
Induce differentiation	miR-9 [20]; miR-124 [21]
Reduce differentiation	miR-128 [22]
Neuronal cells	
Inhibit cell death	miR-223 [23]; miR-181c [24]; miR-592 [25]; miR-424 [26]; miR-23a-3p [27]; miR-23a/b, miR-27a/b, siRNA-Apaf-1 [28]
Promote cell death	miR-134 [29]; miR-200c [30]; miR-30a/b [31–33]; miR-124 [34]; miR-711 [35]
Regulate degeneration and apoptosis	miR-20a [36]; miR-29b [37]; miR-146a, siRNA-miR146a [38]
Promote neurite outgrowth	miR-7 [39]; miR-21 [40]; miR-222, siRNA-PTEN [41]; miR-8 [42]; miR-431 [43]; miR-145 [44]; lncRNA-uc.217 [45]; miR-138, siRNA-SIRT1 [46]
Microglial cells	
Inhibit inflammation	let-7c [47]; miR-124, siRNA-C/EBP-α [48]
Promote pro-inflammation	miR-155 [49]
Inhibit activation	let-7c-5p [50]
Astrocytes	
Promote proliferation	miR-17-5p [51]
Inhibit inflammation	miR-146a [52]
Promote activation and differentiation	miR-181 [24]
Inhibit proliferation and migration	lncRNA-SCIR1 [53]
Schwann cells	
Inhibit proliferation and migration	miR-182 [54]; let-7 [55]; miR-1 [56]
Promote proliferation and migration	miR-221, miR-222 [57]

Table 1 (*continued*)

Cell type and function	ncRNAs
Inhibit migration	miR-9 [58]
Promote migration	miR-132 [59]
Regulate dedifferentiation and proliferation	miR-34a [60]
Regulate myelination	miR-140 [60]; miR-29a [61]
Regulate fibrinolysis	miR-340 [62]
Liver	
Stem/progenitor cells	
Reduce differentiation	let-7b [63]; let-7f [64]
Induce differentiation	miR-1246, miR-1290, miR-148a, miR-30a, miR-30a, miR-424 [65]
Induce/reduce differentiation	miR-122, siRNA-FoxA1 [66–68]
Reduce differentiation and engraftment	miR-199a-5p, siRNA-SMARCA4, siRNA-MST1 [69]
Hepatocytes	
Promote proliferation	miR-21 [70–72]; miR-211 [73]; lncRNA-URHC [74]
Inhibit proliferation	miR-26a [75]; miR-33 [76]; miR-127, siRNA-Bcl6 [77]; miR-378 [70]; lncRNA-H19 [78]
Regulate cholesterol metabolism	lncRNA-HC [79]
Promote migration	lncRNA-HOTAIR [80]
Inhibit apoptosis and inflammation	lncRNA-TUG1 [81]
Cholangiocytes	
Inhibit cell function	miR-506 [82]
Skin	
Epithelial stem cells	
Inhibit proliferation, induce differentiation	miR-203 [83–86]
Induce differentiation	miR-27b, miR-224 [87]; miR-574-3p, miR-31 [88]
Inhibit proliferation	miR-34, siRNA-P63 [89]; miR-720 [90]; miR-210, siRNA-E_2F_3 [91]
Improve proliferation, reduce differentiation	miR-125b, siRNA-$FGFR_2$ [92,93]
Inhibit proliferation, induce differentiation	miR-24, siRNA-PAK4 [94]
Keratinocytes	
Improve migration	miR-205 [95–97]
Inhibit migration, improve proliferation	miR-483-3p [98]
Inhibit migration	miR-198 [99]
Improve migration, inhibit migration	miR-21 [100,101]
Improve migration and proliferation	miR-31, siRNA-EMP-1, siRNA-TGF-β [102]
Regulate apoptosis	lncRNA-p21 [103]
Fibroblasts	
Inhibit proliferation	let-7, miR-125 [104]
Improve proliferation	miR-29 [104]; miR-21 [105]; miR-22 [106]; lncRNA-H19 [107]
Induce senescence	miR-152, miR-181a [108]; miR-141 [109]; miR-143 [110]; miR-519a [111]
Improve migration	miR-21 [112]
Induce epithelial–mesenchymal transition	miR-34 [113]; let-7 [114]
Reduce epithelial–mesenchymal transition	miR-200 [113]
Reduce transdifferentiation	miR-146a [115,116]; miR-7 [117]
Decrease extracellular matrix deposition	miR-29 [118,119]; miR-150 [120]; miR-19a [121]
Increase extracellular matrix deposition	miR-92a [122]
Increase mechano-transduction	miR-21 [123–125]
Control collagen stabilization	lncRNA-TSIX, siRNA-TSIX [126]
Melanocytes	
Inhibit apoptosis	miR-17 [127,128]
Muscle	
Myoblasts	
Induce differentiation	lncRNA-MD1 [129]; miR-1 [130]; lncRNA-MyoD [131]; lncRNA-Dum [132]; lncRNA-MUNC [133]; lncRNA-YY1 [134]; miR-29 [135]; miR-181 [136]; lncRNA-H19 [137]; miR-322, miR-503 [138]
Promote proliferation	miR-133 [130]
Promote proliferation and reduce differentiation	lncRNA-sirt1 AS [139]; lncRNA-Malat1 [31,140]; lncRNA-31 [141]
Reduce differentiation	miR-23a, siRNA-Myh [77]
Promote proliferation and migration	miR-486 [142]
Skeletal muscle satellite cells	
Induce differentiation	miR-206 [143]; miR-214, siRNA-Ezh2 [144]; miR-27b [145]
Inhibit proliferation and induce differentiation	miR-1, miR-206 [146]
Skeletal muscle stem cells	
Inhibit differentiation	miR-669a/q [147]
Induce cell-cycle arrest	miR-195, miR-497 [148]
Cardiac progenitor cells	
Control the balance between differentiation and proliferation	miR-1 [149]
Inhibit proliferation and induce differentiation	miR-133a [150]; miR-1, miR-499 [151]
Enhance cardiac remodeling and reduce survival	miR-208a [152,153]; miR-28b [154]
Inhibit apoptosis	miR-138 [155]

Table 1 (*continued*)

Cell type and function	ncRNAs
Cardiomyocytes	
Inhibit apoptosis	miR-21 [156]; miR-214 [157]; miR-24 [52]; lncRNA-MHRT [158]
Regulate differentiation and remodeling	miR-21, miR-129, miR-212 [159]
Promote hypertrophy	miR-22 [160]
Promote muscle growth	miR-486 [142]
Induce proliferation	miR-199a, miR-590 [161]; miR-17-92 [162]
Inhibit hypertrophy	lncRNA-H19 [163]
Promote apoptosis	lncRNA-NRF [164]
Cardiac fibroblasts	
Inhibit proliferation	miR-101 [165]
Promote proliferation	lncRNA-H19 [166]
Induce reprogramming to cardiomyocytes	miR-1, miR-133, miR-208, miR-499 [167]
Vascular	
Endothelial cells	
Inhibit proliferation	miR-34a [168]; miR-19a [169]; miR-200c, siRNA-ZEB1 [170]
Promote proliferation and/or migration	miR-126-5p [171]; miR-210 [172]; miR-424 [173]; lncRNA-H19 [81]
Induce senescence and reduce angiogenesis	miR-34a [168]; miR-217 [174]; miR-17-92 [175]; miR-503 [176]; siRNA-ROBO4 [177]
Inhibit migration and angiogenesis	miR-101, siRNA-EZH2 [178]
Promote angiogenesis	miR-17-5p, miR-18a, miR-31, miR-155 [179]; miR-210 [172]; miR-424 [173]; lncRNA-H19 [81]; miR-126 [180]
Promote apoptosis and senescence	miR-200c, siRNA-ZEB1 [170]; PINC [181]
Inhibit proliferation, migration, and apoptosis	miR-503 [176]; miR-155, siRNA-RhoA, siRNA-MYLK [182]
Regulate inflammation	miR-92a, siRNA-KLF4 [183]; miR-663 [184]; miR-10a [185]; miR-712, miR-502, siRNA-TIMP3, siRNA-RECK [186]
Smooth muscle cells	
Induce differentiation and inhibit proliferation	miR-143, miR-145 [187]; lncRNA-MYOSLID [166]
Inhibit proliferation, migration, and apoptosis	miR-503 [176]
Promote migration	miR-712, miR-502, siRNA-TIMP3, siRNA-RECK [186]; miR-24, siRNA-Trb3 [188]
Promote proliferation	miR-24, siRNA-Trb3 [188]; miR-221, miR-222, siRNA-Kip1, siRNA-Kip2 [189]; miR-34a [190]
Promote proliferation and inhibit apoptosis	miR-21 [191]
Inhibit proliferation and promote apoptosis	lncRNA-HIF1A-AS1 [33]; lncRNA-p21 [192]
Reduce elastin levels	miR-29a [193]
Regulate phenotype	siRNA-Jagged1 [194]
Fibroblasts	
Reduce elastin levels	miR-29a [193]
Stem cells	
Induce differentiation	miR-145 [195]; miR-200c, miR-150, siRNA-ZEB1 [196]; miR-1 [197]; miR-10a [198]
Reduce differentiation	siRNA-NOX4, siRNA-TGF-β [199]
Endothelial progenitor cells	
Inhibit survival and migration	miR-15a, miR-16 [200]

2.1.2. Neuronal cells

After nerve injury, neuronal death is one of the events that influences recovery; therefore, protecting neurons from cell death is important. miR-223, miR-181c, miR-592, miR-424, miR-23a-3p, miR-23a/b, and miR-27a/b can protect neurons from cell death after ischemic brain injury [23–28], while miR-134, miR-200c, miR-30a/b, miR-124, and miR-711 promote neuronal cell death [29–32,34,35,201]. In spinal cord injury, miR-20a causes motor neuron degeneration by targeting *Ngn1* [36], and miR-29b regulates neuronal apoptosis by reducing the expression of Bad, Bim, Puma, and Noxa [37]. Following peripheral nerve injury, overexpression of miR-21 and miR-222 reduces apoptosis and enhances the viability of cultured dorsal root ganglion (DRG) neurons [40,41]. miR-146a mediates apoptosis in DRG neurons under hyperglycemic conditions [38].

The outgrowth of neurites/axons from lesioned neurons is the essence of peripheral nerve regeneration. miR-21 and miR-222 promote neurite outgrowth by targeting Sprouty2 and PTEN, respectively [40,41]. miR-8, miR-431, miR-145, and miR-138 have been shown to play regulatory roles in neurite outgrowth [42–44,46]. In addition, lncRNA-uc.217 regulates neurite outgrowth in DRG neurons following peripheral nerve injury [45].

2.1.3. Neuroglial cells

Microglial cells: Microglial cells are important cell types in the CNS. let-7c suppresses the activation of microglial cells against ischemic damage [47]. miR-124 can decrease the inflammatory response toward nerve injury in order to prevent secondary injury in microglial cells [48]. miR-155 regulates the M1/M2 phenotype ratio, and further regulates the microglia-mediated neurotoxic response and enhanced axonal regeneration [49].

Astrocytes: Astrocytes, which are specialized glial cells, carry out supportive, metabolic, and homeostatic functions in the CNS. The injury of myelinated axons results in axonal degeneration and the accumulation of myelin debris, which contains a variety of axonal growth inhibitors. Removal of these inhibitors via microglia and astrocytes can facilitate axon regeneration. Astrocytes also affect the immune response by mediating different signaling pathways. miR-17-5p promotes the proliferation of astrocytes by targeting the cell-cycle inhibitors p21 and RB1 [51]. miR-181 affects inflammatory cytokine secretion of astrocytes, and modulates astrocyte activation and differentiation [24]. miR-146a carries out an anti-inflammatory role by regulating the release of cytokines from astrocytes, suggesting that miR-146a treatment has the potential to prevent secondary injures and promote tissue repair [52].

Schwann cells (SCs): SCs are the main glial cells in the PNS and play an essential role in peripheral nerve regeneration. SCs can also produce a high level of different GFs such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and so forth [202]. In addition, SCs possess the capacity of phagocytosis to clear away myelin debris. These characteristics make SCs the most widely used support cells in neural tissue engineering for peripheral nerve regeneration. SCs are able to dedifferentiate back to an immature-like state following axonal damage. After dedifferentiation, SCs increase their cell number by proliferation in order for the repair process to begin. The migration of SCs to injured sites is also necessary in order for them to carry out their

functions. Therefore, enhancing the efficiency of SC proliferation and migration during this preparation phase may promote nerve regeneration. miR-182 inhibits the proliferation and migration of SCs by targeting FGF9 and NTM, respectively, at an early stage following sciatic nerve injury [54], while miR-221 and miR-222 promote the proliferation and migration of SCs by targeting *LASS2* [57]. miR-9 is an important functional regulator of SC migration by targeting CTHRC1, which in turn regulates Rac1 GTPase [58]. Overexpression of miR-132 facilitates SC migration in order to regulate peripheral nerve regeneration [59]. miR-34a can regulate SC dedifferentiation and proliferation following peripheral nerve injury by targeting Notch1 and cyclin D1 [60].

NGF, the first-discovered member of the neurotrophin family, contributes to neuronal survival and axon growth of the PNS, and ensures the functional integrity of neurons in the CNS. Many experimental studies have determined the beneficial effects of NGF on nerve regeneration. However, clinical applications of NGF are still limited by several constraints, including its deleterious side effects and the complexity of its delivery. let-7 miRNAs have been found to significantly regulate cell proliferation and migration of primary SCs by targeting *NGF* and suppressing its protein translation. Inhibition of let-7 miRNAs increases NGF secretion from primary cultured SCs, and enhances axonal outgrowth from a co-culture of primary SCs and DRG neurons. The inhibitory effect of let-7 miRNAs on SC apoptosis may also serve as an early stress response to nerve injury [55]. In addition, NGF expression that is inhibited by let-7 miRNA can regulate miR-221/222 expression in order to affect the SC phenotype, suggesting that a cascade of let-7 miRNA, through NGF, to miR-221/222 may represent a bypass for the let-7 regulation of SC phenotype modulation. Another neurotrophin, BDNF, is regulated by miR-1, and miR-1 regulates the proliferation and migration of SCs [56].

SCs are responsible for synthesizing myelin sheath in the PNS. miR-140 can modulate axonal myelination in co-cultures of DRG neurons and SCs by targeting the transcription factor Egr2, a master regulator of myelination [60]. miR-29a may regulate the myelination of SCs by targeting PMP22, a dose-sensitive, disease-associated protein primarily expressed in myelinating SCs [61].

After peripheral nerve injury, the degenerative debris and inflammatory alterations at the injury site may block the elongation of regenerating axons from reaching target organs. miR-340 regulates fibrinolysis, and also influences debris removal and axonal regrowth during sciatic nerve regeneration by targeting tPA, a serine protease with the capability of degrading matrix molecules and cell adhesions [62].

2.2. Liver tissue engineering

The liver is one of the largest organs in the human body. Acute or acute-on-chronic failure of the liver results in a life-threatening situation. Survival rates have improved substantially in recent years through advances in critical-care management and the use of liver transplantation. Unfortunately, the number of available liver grafts does not meet the continuously growing need [203,204]. The use of bioengineered livers, instead of procuring organs from brain-dead donors or removing parts of the liver from living donors, is the most promising approach for liver support [205].

Tissue-engineered solutions are under development to temporarily or definitively support or replace a diseased liver. Studies have shown that differentially expressed ncRNAs in the liver are associated with several physiological and pathological processes [206–210]. Some reports have suggested that ncRNAs could improve hepatocyte proliferation or induce the differentiation of stem cells into hepatocyte-like cells (Table 1). miR-21 and miR-378 promote DNA synthesis in hepatocytes after a partial (2/3) hepatectomy by inhibiting Btg2 and ornithine decarboxylase, respectively [70]. miR-21 can regulate liver regeneration by influencing the progression through G1 and into the S phase of the cell cycle, by targeting cyclin D1 [71]. The inhibition of miR-33 can obviously increase liver regeneration [76]. miR-26a and miR-127 also regulate hepatocyte proliferation [75,77,211].

The differentiation of stem cells or other types of progenitor cells to hepatocyte-like cells is the second major field in which ncRNAs are already in use, with potential applications for liver tissue engineering. The overexpression of miR-122 can improve hepatic differentiation [66,212], and miR-122 expression gradually increased during the maturation of mouse embryonic stem cells toward hepatocytes [68]. let-7 can regulate the secretion of hepatic-specific factors in human adipose-tissue-derived MSCs [63]. Using a set of miRNAs instead of a single miRNA is another approach to optimize hepatic differentiation. Overexpression of seven miRNAs (miR-1246, miR-1290, miR-148a, miR-30a, miR-424, miR-542-5p, and miR-122) induced human MSC (hMSC) conversion into functionally mature hepatocytes, while a single miRNA could not initiate hepatic differentiation [65].

Compared with the hepatocyte system, less-extensive attention has been paid to the biliary tree. Tissue engineering approaches mimicking biliary function would require a more complex microarchitecture of scaffolds that enable cell-cell interactions, allowing for biliary metabolism and transport [213,214]. Although little is known about the role of miRNAs in regulating cholangiocyte proliferation and function [215], several studies implicated specific miRNAs in the pathogenesis of cholangiocarcinoma. For example, the overexpression of miR-31 in cholangiocarcinoma cells altered RAS/MAPK signaling [216], and miR-138 can regulate cholangiocarcinoma proliferation, cell-cycle control, and migration, possibly by directly targeting RhoC [217]. miR-506 regulates the expression of anion exchanger 2 (AE2), and the suppression of miR-506 leads to improved AE2 function in primary biliary cirrhosis cholangiocytes [82]. In addition, the regulation of miR-125b/let-7a expression in cholangiocytes could be a therapeutic approach for biliary diseases [218].

2.3. Skin tissue engineering

The demand for clinical intervention for skin loss has increased in recent years. Tissue engineering represents a feasible approach to obtain replacement skin. A key point in the development of engineered skin is controlling cellular behavior. As a new and exciting field of RNA interference, ncRNAs have emerged to overcome the barriers of engineered skin design. The regulation of cell behavior by ncRNA modulation provides a realistic and precise method of affecting cell behavior in bioengineered skin equivalents. Generally speaking, miRNAs may be modulated by overexpression or silencing in skin tissue engineering [219]. The marriage of ncRNA with skin tissue engineering offers the promise of creating safer, more effective skin tissue engineering for critically important clinical conditions [220].

Epithelial stem cells are skin-specific, making them the ideal choice for skin tissue engineering. miRNA can govern the transition of epithelial stem cells from proliferative pools to differentiated keratinocytes [221]. miR-203 plays an important role in maintaining "stemness" in the skin and in other stratified epithelial tissues [222–224]. In addition, miR-203, miR-720, and miR-574-3p can regulate the initiation of epithelial stratification and the maintenance of basal keratinocyte proliferation by directly targeting p63 [89,90].

Keratinocytes, which differentiate from epithelial stem cells, are the key cells that provide a barrier function to the skin. miR-

205 can regulate the migration of keratinocytes [95,96], and miR-198 and miR-21 were found to be associated with chronic wound healing by regulating the migration of keratinocytes [99]. miR-31 promoted the migration and proliferation of keratinocytes [102], and miR-483-3p can affect the growth arrest of keratinocytes during the final steps of re-epithelialization [225].

Fibroblasts are the primary cells of the dermis. let-7 plays an important function in dermal fibroblast proliferation in serum-starved quiescent fibroblasts [104]. miR-22 promotes the proliferation of fibroblasts by regulating several cell-cycle genes [106]. Faraonio et al. [226] described how 24 miRNAs influence senescence-dependent changes in human diploid fibroblasts. Of these, miR-210, miR-376a, miR-486-5p, miR-494, and miR-542-5p can enhance DNA damage and promote senescence. miR-21 was found to regulate fibroblast migration, which is critical to the success of skin tissue engineering [100,101].

It has also been reported that melanocytes can be incorporated into epidermal and dermoepidermal bioengineered skin equivalents [227]. Several studies have shown that some miRNAs could affect the development and progression of melanoma [228–230]. miR-17 has the ability to partially rescue the apoptosis of melanocytes after Dicer ablation by targeting Bim [127]. miR-137, miR-182, and miR-340 can regulate microphthalmia-associated transcription factor in melanoma cells [231–233].

2.4. Muscle tissue engineering

In the human body, muscles develop strength and body work, and are responsible for constant blood pumping (i.e., the cardiac muscle) and posture and movements (i.e., the skeletal muscles). Muscle injury and degeneration account for significant fractions of the global adult mortality and disease burden [234].

Regenerative treatments are not always available for the clinical care of striated muscle disorders; therefore, muscle tissue engineering and stem-cell-based treatments are being promisingly explored. The aim of tissue engineering is the functional recovery of damaged striated muscles by combining biocompatible scaffolds with bioactive molecules and/or cells [235,236]. ncRNAs are emerging as key players in regulating the phenotype of seed cells and the adaptability of both exogenous and resident stem cells [129]. Thus, the roles of ncRNAs (mainly miRNAs) are widely reported in the development of skeletal and cardiac muscle, and in regulating the regenerative potential of muscle progenitors (Table 1).

Studies have shown that muscle-related miRNAs, such as miR-1, miR-133, and miR-206, play a critical role in modulating muscle formation and regeneration [237]. miR-1 promotes differentiation of cultured myoblasts by targeting HDAC4, while miR-133 stimulates myoblast proliferation, mostly through the repression of Srf expression [130]. miR-206 improves skeletal muscle regeneration in Duchenne muscular dystrophy [143] and slows the progression of amyotrophic lateral sclerosis [238]. In addition, lncRNA-MD1 serves as a competing inhibitor to titrate miR-133 and miR-135 away from their targets, MAML1 and MEF2C, further influencing myoblast differentiation [129].

At present, the seed cells of tissue engineering for muscle repair are often stem cells; these provide the degenerating muscle tissue with progenitors to reconstitute genetically suitable myocytes and restore functionality. Sato et al. [148] showed that the transplantation of skeletal muscle stem cells (MuSCs), which were treated with miR-195 and miR-497, improved the efficiency of muscle regeneration through target genes involved in the cell-cycle progression in dystrophin-deficient mice.

miRNAs are found to play an important role in cardiac tissue, where they stimulate cardiomyocyte proliferation in neonatal mice, rat hearts, and adult mice following myocardial infarction [161]. miRNAs can carry out entwined spatiotemporal roles in the expansion and terminal differentiation of cardiac progenitor cells (CPCs). For example, miR-1 inhibits the expansion of cardiac progenitors by targeting *Hand2*, while miR-1-lacking murine embryos die at embryonic day (E) 10.5 because of severe cardiac malformations [149]. The regulatory role of miRNAs has also been reported in the aberrant switch of fetal programs in response to cardiac stress; miR-21, miR-129, and miR-212 led to hypertrophy and reactivation of a fetal cardiac gene program in rat neonatal cardiomyocytes [159]. As in skeletal myogenesis, miR-22 and miR-133a can affect hypertrophic remodeling by regulating key epigenetic regulators in cardiomyocytes [239].

Overall, as a tissue engineering strategy, the combination of MuSCs, postnatal cardiomyocytes or cardiac stem cells treated with selected ncRNAs, and biomimetic scaffolds should be able to improve their respective engraftment in the damaged tissue, which may make it possible to increase tissue regeneration ability in skeletal muscle disorders and heart diseases, respectively [240].

2.5. Vascular tissue engineering

The vascular system forms an extensive network throughout the body, mediating gas exchange, nutrient transport, and waste removal, as well as delivering cells and mediators in the immune response [241,242]. Vascular tissue engineering is based on the use of scaffolds that can be combined with seed cells such as stem cells, along with other cellular and molecular products, to build vascular conduits, which can be used to restore, maintain, or improve vascular tissue function [241]. In vascular tissue engineering, ncRNAs can enhance the quantity or quality of cells available for cell-based therapeutic angiogenesis, promote stem cell differentiation to vascular cells to be seeded in the scaffolds, improve the function of cells acting at different levels in the vascular scaffold, and correct antiangiogenic molecular defects [243,244].

Endothelial cells (ECs) and smooth muscle cells (SMCs) are essential components of blood vessels; thus, ECs and SMCs are regarded as the main supporting cells in vascular tissue engineering. For this reason, ncRNA application in vascular tissue engineering mainly focuses on the regulatory roles of ncRNAs toward these two cells. ECs line the inner layer of the entire vascular system and ensure vascular homeostasis. They have an essential role during developmental and post-natal angiogenesis [241]. miR-34a and miR-217 promote endothelial senescence, and their inhibitor reduces senescence and increases angiogenesis [168,174]. miR-424, miR-17-5p, miR-18a, miR-31, and miR-155 promote vascular integrity and angiogenesis [173,179]. miR-210 and miR-126-5p promote the proliferation of ECs [171,172]. In addition, ncRNAs can be applied alone or in combination with GFs in order to improve endothelial coverage and endothelial function in vascular tissue engineering.

SMCs make up the middle layer of the vascular wall, and perform the physiological functions of contracting and relaxing vessels and regulating blood pressure and blood flow distribution. They also play important roles in the vascular remodeling processes that follow injury [245–247]. Following vascular injury, SMCs dedifferentiate to promote vessel repair. Healthy SMCs should return to their contractile phenotype once the injury is resolved [246]. While miR-221, miR-222, and miR-24 promote SMC proliferation, miR-143 and miR-145 stimulate differentiation.

miRNAs also regulate the process of stem cell differentiation to vascular cell, and the functional capacities of vascular progenitor cells. Some studies focused on techniques to promote vascular differentiation from stem cells; for example, miR-1, miR-10, and miR-

145 can regulate stem cell differentiation to vascular lineages [195].

To sum up, ncRNAs carry out important roles in the cells associated with tissue engineering; therefore, they may have potential therapeutic applications in tissue engineering as regulators of the function and phenotype of some seed cells. Table 1 provides more information about regulation relationships.

3. Application methods

It is now widely recognized that an effective and safe delivery system is key to ncRNA application in tissue engineering. In brief, an ncRNA delivery system should ensure low cytotoxicity and high transfection efficiency, and should also allow controlled release of ncRNAs during the lengthy process of tissue regeneration [248]. Here, we focus on some delivery methods of ncRNAs that have proven useful for tissue engineering applications, according to available works in the literature (Fig. 1).

3.1. Viral transduction

Due to the high transfection efficiency, viral transduction is a good choice for delivering ncRNAs. Several viruses such as retroviruses, lentiviruses, adenoviruses, and adeno-associated viruses (AAVs) can be used in tissue engineering; retroviruses and lentiviruses are widely used.

Retroviruses can be used effectively in various types of dividing cells, including NSPCs. However, the drawback of retroviruses is their inability to infect quiescent cells [249]. In contrast, lentiviruses can transduce non-dividing cells [250–253], which makes these viruses popular for use in the transfection of cells for tissue engineering. The drawbacks of using retroviruses and lentiviruses are that these viruses are unstable when kept in storage and are unable to achieve high viral titers. Adenoviruses can efficiently achieve high viral titers in dividing and non-dividing cells; however, they have significant immunogenicity and toxicity [254,255]. AAVs are a safe and efficient method for the delivery of ncRNAs because of their small size. AAVs are stable in the nucleus, and can maintain high levels of gene expression for months or years [254].

Of these methods, viral transduction provides high transfection efficiency and sustained expression of ncRNAs in transfected cells due to the integration of the viral genome into the host genome. However, genomic integration can lead to uncontrolled insertional mutagenesis, so the use of viral-mediated ncRNA delivery in translational therapeutic applications is limited [256–258].

3.2. Non-viral transduction

In comparison with viral transduction, non-viral delivery methods have unique advantages, including low immunogenicity and mutagenesis, and the capacity of delivering a large quantity of therapeutic agents [256]. Hence, researchers often prefer non-viral approaches to viral transduction.

The liposome is widely used in methods of ncRNA delivery. Its advantages are its biocompatibility, reproducibility, and ease of large-scale production [259]. A number of conventional reagents are currently available, including Lipofectamine®, siPORT™, HiPerFect, Oligofectamine™, MaxSuppressor™, DharmaFECT®, SilentFect™, and NeuroPorter™. Despite their variation in structure, these reagents share some common features [256]. In particular, they contain positively charged groups, which interact with the negatively charged sugar-phosphate backbone of RNA molecules. This interaction helps the contact between the RNA/reagent complex and the cell membrane, thereby promoting subsequent cellular uptake [260]. However, lipid-based delivery systems cause toxicity and nonspecific uptake *in vivo*. Moreover, this toxicity, which is accompanied by gene changes, could in turn hinder the desired outcome of the application [261].

Numerous polymers such as poly(lactide-*co*-glycolide) (PLGA) and polyethylenimine (PEI) are also commonly used as ncRNA

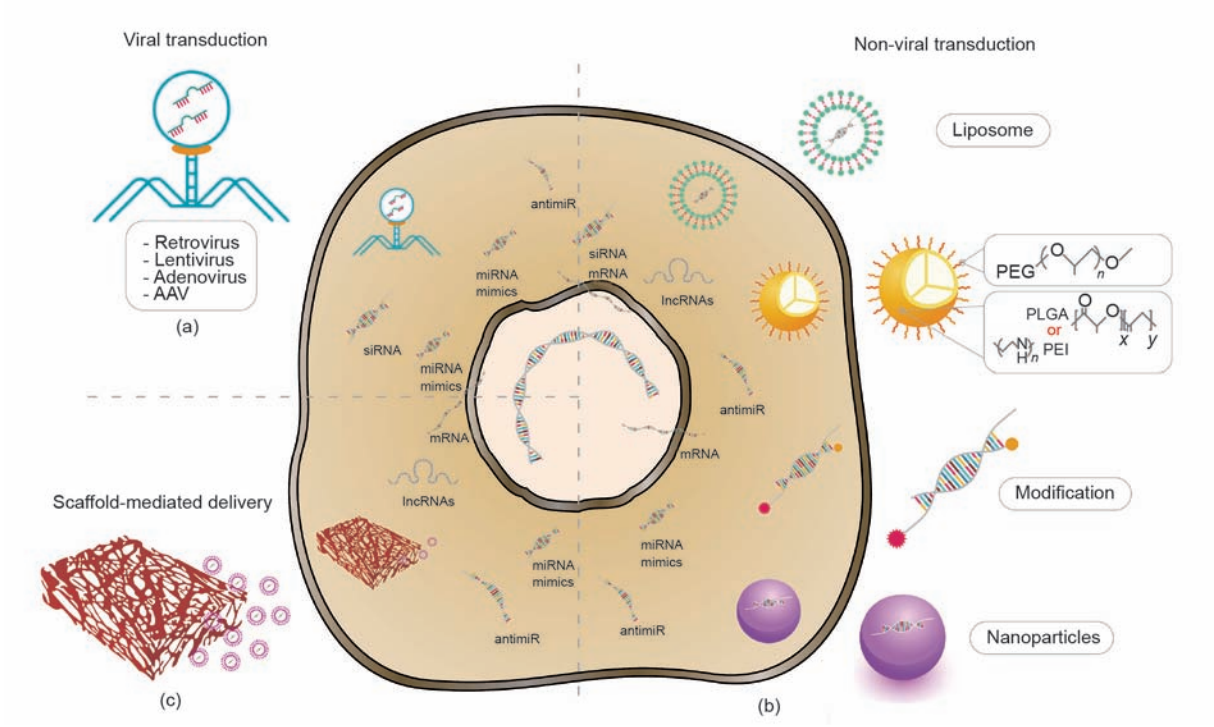

Fig. 1. Schematic illustration of ncRNA delivery. (a) Viral transduction of ncRNAs into cells through virus infection using different viral vectors; (b) non-viral transduction through: liposomes; polymers including polyethylene glycol (PEG), poly(lactide-*co*-glycolide) (PLGA), and polyethylenimine (PEI); chemical modification; or nanoparticles; by which ncRNAs are taken into cells, mainly by cell endocytosis with the help of the above carriers; (c) scaffold-mediated delivery, in which ncRNAs are released into cells from a scaffold loaded with non-viral ncRNA vectors, followed by matrix degradation to enable cell ingrowth.

carriers for gene therapy [262]. PLGA has been widely used for drug delivery because it is safe, biocompatible, and biodegradable. In addition, it can be further optimized to control pharmacodynamics via the surface modification of PLGA nanoparticles [248]. PLGA-based nanoparticles are a potential approach for efficient ncRNA delivery. PEI, another widely used material for ncRNA delivery, is water-soluble and positively charged. The positively charged PEI can encapsulate negatively charged ncRNAs by electrostatic interaction. After endocytosis of these nanocomplexes, the strong buffer effect of the complex results in endosome swelling, and subsequently causes endosome destabilization and the release of ncRNA-encapsulated nanoparticles into the cytosol [262–265].

Several chemical modifications can enhance the stability and affinity of ncRNAs, and thus improve systemic delivery efficacy by increasing the degradation resistance of nucleases in cells and tissues. For example, the 2′-*O*-methyl, 2′-*O*-methoxyethyl, or 2′-*O*-fluorol ncRNAs produced by 2′-OH group modification have enhanced stability and higher binding affinity [266]. Cholesterol was also conjugated into these chemical modifications in order to improve the cellular uptake of ncRNAs; many papers reported that cholesterol-conjugated ncRNAs can enter cells directly via intravenous injection or tissue injection.

3.3. Scaffold-mediated delivery

Scaffold-mediated delivery is another common delivery method in tissue engineering and regenerative medicine. For cell engraftment, proliferation, differentiation, and migration at the injured site, biomimetic scaffolds provide a proper microenvironment for tissue repair and regeneration [240]. In addition, topographical features of scaffolds can ensure the sustained delivery of genes and perform additional physical signals to regulate cellular behavior and gene-uptake efficiencies [256]. Moreover, scaffold-mediated delivery can improve local therapy, thus directly enhancing the dose in the target tissue relative to an off-target site. Scaffold architecture also affects cell phenotype. For example, fiber scaffolds—particularly those with aligned fibers—can regulate the maturation of SCs [256,267]. A number of studies have demonstrated the delivery of ncRNAs from tissue engineering scaffolds, thus introducing a novel method for the regulation of gene expression from the delivery platform [220].

4. Concluding remarks and future perspectives

4.1. Potential risks of ncRNA-based therapy

ncRNA therapeutics, a new concept that differs from conventional chemical drug design, has emerged in recent years in treatment involving tissue engineering and regenerative medicine. However, numerous challenges exist for the therapeutic application of ncRNAs in tissue engineering and regenerative medicine. For example, although the fact that miRNAs target multiple target genes can be an advantage, it also causes ambiguity regarding the scope of the exact genes that are regulated by miRNAs. For clinical evaluation, the functional phenotype and regulatory mechanisms of an miRNA need to be well elucidated and validated. Because of their regulation of a wide variety of cellular events for tissue regeneration, the diversified effects of miRNAs need to be carefully controlled [268]. For example, miR-221 and miR-222 not only affect the proliferation and migration of SCs by regulating *LASS2*, but also regulate the aggressive growth of human glioblastomas by targeting $p27^{Kip1}$ [57,269].

For the application of lncRNAs, the challenges are even greater. lncRNAs can regulate a series of cellular processes including proliferation, differentiation, migration, survival, and apoptosis through diverse mechanisms; however, identification of the functioning mechanisms is limited [270]. In addition, lncRNAs are tissue-specific protein-coding genes, resulting in additional challenges when targeting ncRNAs to a specific tissue or to subcellular compartments.

For ncRNAs with well-defined molecular regulation mechanisms, the delivery system is the greatest challenge. The pathways underlying the delivery process are not well elucidated; therefore, the established guidelines may not always lead to the expected biological phenomenon—a problem that needs to be solved.

4.2. Future perspectives

Tissue engineering generates biological substitutes to replace compromised tissues or organs mainly by means of scaffold-based implants, through which seed cells are often introduced. The concomitant introduction of ncRNAs for phenotype modulation of the seed cells is also suggested. To date, siRNAs have been used in diverse scaffold-based tissue engineering strategies; however, the application of other ncRNAs, especially miRNAs, is just beginning.

Although some interesting studies have illustrated the application of ncRNAs in tissue engineering, a better comprehension of the effects and specific targets of ncRNAs in different types of tissues remains to be achieved in view of ncRNA-based therapeutics. In addition, the development of a delivery system to protect ncRNAs against degradation, and to enable them to reach the target tissue/organ, is a major hurdle to overcome. To fulfill these goals, a close collaboration among specialists from different research areas, including medical science, biology, and engineering, is required.

In conclusion, research on ncRNA applications in tissue engineering is still in its infancy. However, ncRNA-based therapy is developing rapidly and has provided a new horizon for tissue engineering strategies in transporting ncRNA safely into seed cells. Given an improved understanding of ncRNA biology and ncRNA delivery, we believe that the utility of ncRNAs in tissue engineering and regenerative medicine will be dramatically improved in the near future.

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Compliance with ethics guidelines

Shiying Li, Tianmei Qian, Xinghui Wang, Jie Liu, and Xiaosong Gu declare that they have no conflict of interest or financial conflicts to disclose.

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