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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]