International Journal of Pharmaceutics 524 (2017) 312–329

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Prospects of siRNA applications in regenerative medicine☆

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A R T I C L E I N F O

Article history:
Received 5 December 2016
Received in revised form 14 March 2017
Accepted 31 March 2017
Available online 4 April 2017

Keywords:
Tissue engineering
siRNA
Gene expression
Delivery systems

A B S T R A C T

Small interfering RNA (siRNA) has established its reputation in the field of tissue engineering owing to its ability to silence the proteins that inhibit tissue regeneration. siRNA is capable of regulating cellular behavior during tissue regeneration processes. The concept of using siRNA technology in regenerative medicine derived from its ability to inhibit the expression of target genes involved in defective tissues and the possibility to induce the expression of tissue-inductive factors that improve the tissue regeneration process. To date, siRNA has been used as a suppressive biomolecule in different tissues, such as nervous tissue, bone, cartilage, heart, kidney, and liver. Moreover, various delivery systems have been applied in order to deliver siRNA to the target tissues. This review will provide an in-depth discussion on the development of siRNA and their delivery systems and mechanisms of action in different tissues.
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☆ The authors declare no conflict of interest.
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http://dx.doi.org/10.1016/j.ijpharm.2017.03.092
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1. Introduction

Tissue engineering is a multidisciplinary science that applies different strategies based on various cell types and scaffolds to regenerate injured tissues and restore their normal behavior (Barry and Murphy, 2004; Leor et al., 2003; Mottaghitalab et al., 2013b; Shokrgozar et al., 2011). The initial approach in tissue engineering was to use *de novo* engineering to prepare appropriate structures for implantation (Hassani Besheli et al., 2017; Mottaghitalab et al., 2015). To fabricate suitable structures that can mimic natural tissues, tissue engineering applies principles of mechanical and chemical engineering and biomaterial science (Fisher and Mauck, 2013; Norouzi et al., 2013; Shahverdi et al., 2014). However, it is essential to consider whether such engineered constructs are capable of inducing cellular proliferation, migration, and differentiation, leading to optimal tissue regeneration (Farokhi et al., 2013, 2014; Mottaghitalab et al., 2011, 2013a). To augment the advantages of tissue engineering strategies for mimicking the structure of natural tissues, new methodologies have been introduced that use nucleic acid therapeutics as inducing biomolecules to improve regeneration processes of injured tissues (Kiani et al., 2016; Tekie et al., 2015). Many nucleic acid-based biomolecules have been used for these purposes; however, small-interfering RNA (siRNA) has established its reputation in regenerative medicine owing to its potential to suppress regulatory genes that prevent normal tissue regeneration processes. siRNA can also be used to target specific genes responsible for triggering signaling pathways involved in tissue repair (Eivazy et al., 2016; Jadidi-Niaragh et al., 2016). Therefore, siRNA can play an important role in manipulating cellular pathways that lead to optimal tissue regeneration (Bertrand et al., 2002). siRNA based therapeutics employ different mechanisms of action to silence specific regulatory genes in different tissues. Here, we explain the most important siRNA-based silencing mechanisms for genes involved in different tissues, such as heart, kidney, liver, bone, cartilage, and nervous tissue. Moreover, various systems have been developed for delivering siRNA to desired tissues (Amarzguioui et al., 2003; Chiu and Rana, 2003; Czauderna et al., 2003) and they are discussed in detail in this review. Owing to the recent employment of siRNA in regenerative medicine, many researchers have focused on using these biomolecules to elucidate how these molecules could improve the regeneration of various types of tissues. However, to our knowledge, no comprehensive review of the literature has been conducted on this issue yet. Therefore, we highlight some of the recent advances in siRNA-based therapeutics in regenerative medicine.

2. Skin regeneration

Skin is a multilayered organ with the ability to protect the body against external aggressions such as ultraviolet (UV) radiation, trauma, temperature extremes, toxins, and microbial contaminations. Skin is comprised of three main layers including epidermis, dermis, and subcutaneous tissue that are responsible for the high turnover capacity of this tissue. Epidermis is the outer layer of skin that creates a waterproof barrier on the surface of the body that is coated with a keratinized layer, stratum corneum; while, dermis is a tough connective tissue containing hair follicles and sweat glands located beneath the epidermis. Subcutaneous tissue is the deeper layer of skin that mostly contains fatty and connective tissues. Skin has some beneficial activities for the body such as immunologic surveillance, thermoregulation, sensory function, and controlling the loss of insensible fluid (Fig. 1) (Addis and Epstein, 2013; Blanpain, 2010; Gurtner et al., 2008). There are many strategies for skin repair such as autografts, allografts, tissue-engineered scaffolds, and wound dressings (Geusens et al., 2009). siRNA therapeutics are also potent alternative to the conventional methods for skin regeneration owing to their accessibility in the body (Layliev et al., 2012; Mirdailami et al., 2015; Norouzi et al., 2015).

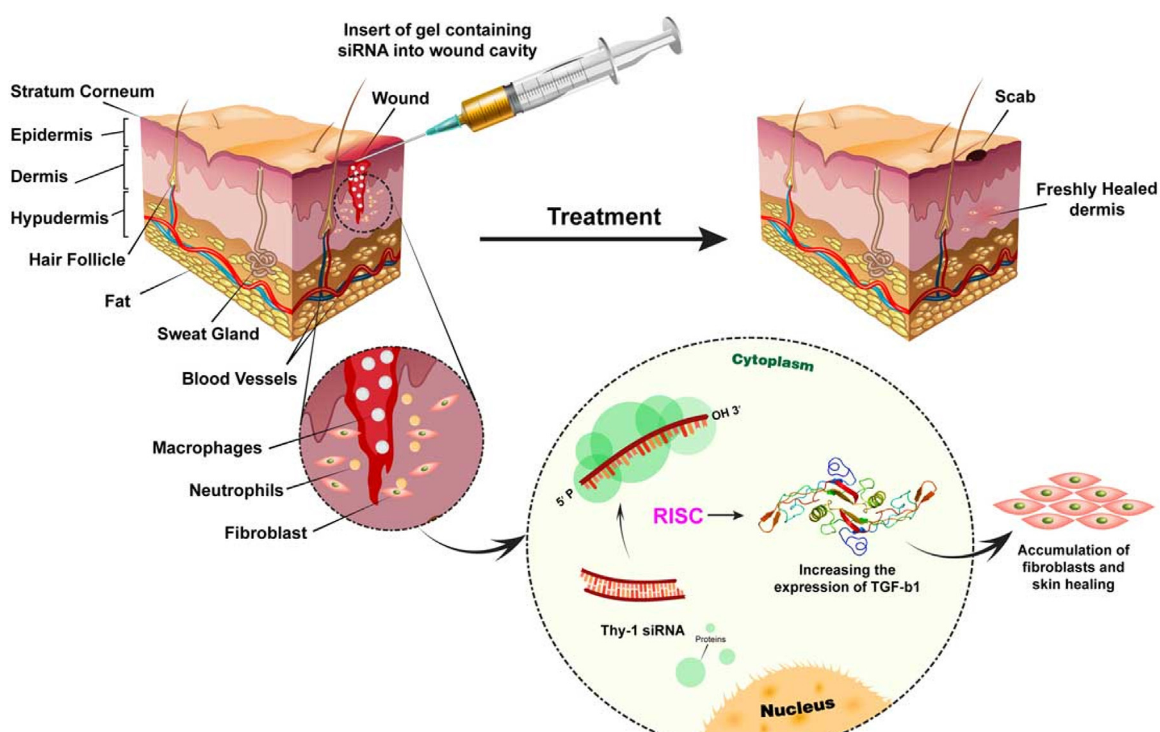

Fig. 1. Schematic representation of skin tissue and the siRNA based mechanisms for skin regeneration.

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