Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biomedical Engineering

Regeneration mechanism for skin and peripheral nerves clarified at the organ and molecular scales

Ioannis V. Yannas[a,b], Dimitrios S. Tzeranis[a,c] and Peter T. C. So[a,b]

Abstract

This article is a review of current research on the mechanism of regeneration of skin and peripheral nerves based on use of collagen scaffolds, particularly the dermis regeneration template (DRT), which is widely used clinically. DRT modifies the normal wound healing process, converting it from wound closure by contraction and scar formation to closure by regeneration. DRT achieves this modification by blocking wound contraction, which spontaneously leads to cancellation of scar formation, a process secondary to contraction. Contraction blocking by DRT is the result of a dramatic phenotype change in contractile cells (myofibroblasts, MFB) which follows specific binding of integrins $\alpha_1\beta_1$ and $\alpha_2\beta_1$ onto hexapeptide ligands, probably GFOGER and GLOGER, that are naturally present on the surface of collagen fibers in DRT. The methodology of organ regeneration based on use of DRT has been recently extended from traumatized skin to diseased skin. Successful extension of the method to other organs in which wounds heal by contraction is highly likely though not yet attempted. This regenerative paradigm is much more advanced both in basic mechanistic understanding and clinical use than methods based on tissue culture or stem cells. It is also largely free of risk and has shown decisively lower morbidity and lower cost than organ transplantation.

Addresses

[a] Department of Mechanical Engineering Massachusetts Institute of Technology, Cambridge, MA 02139, USA

[b] Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Corresponding author: Yannas, Ioannis V, Department of Mechanical Engineering Massachusetts Institute of Technology, Cambridgem, MA 02139, USA. (yannas@mit.edu)

[c] Present Address: Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion 70013, Greece

Current Opinion in Biomedical Engineering 2018, **6**:1–7

This review comes from a themed issue on **The Future of Tissue Engineering**

Edited by **Carlijn Bouten, Leda Klouda and Katja Schenke-Layland**

Received 10 November 2017, revised 10 December 2017, accepted 14 December 2017

https://doi.org/10.1016/j.cobme.2017.12.002

Keywords

Regeneration, Skin, Peripheral nerves, Phenotype change, Contraction blocking, Integrin-ligand interaction.

Abbreviations

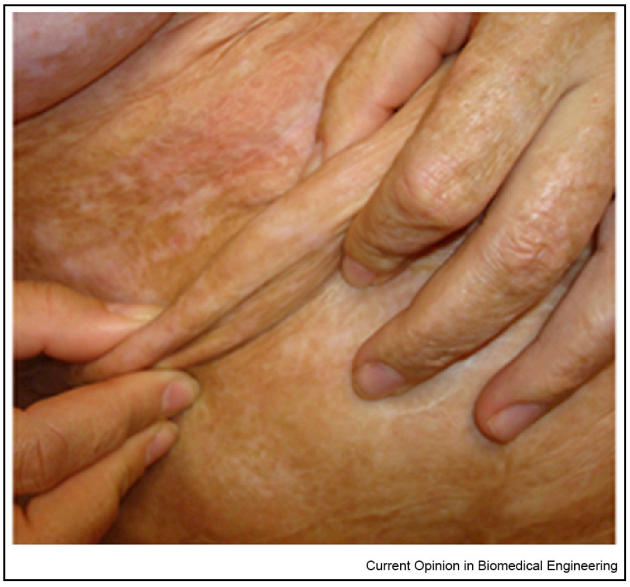
DRT, dermis regeneration template; MFB, myofibroblasts; GFOGER, glycine-phenylalanine-hydroxyproline-glycine-glutamic acid-arginine; GLOGER, glycine-leucine-hydroxyproline-glycine-glutamic acid-arginine; PN, peripheral nerve; αSMA, alpha smooth muscle actin.

Introduction

Researchers have spent substantial efforts during the past decades to generate physiologically functioning organs *in vitro*. These efforts have been based on culturing cells of various types, often with added growth factors, and on use of a large variety of biomaterials, typically in the form of gels and scaffolds, but without sufficient success to warrant routine clinical use. In a different approach, stem cell methodology has been advanced as a potentially revolutionary approach that would ideally recapitulate biological development and grow organs thereby; however, dependable clinical translation has not been achieved yet.

In contrast, grafting of wounds in skin and peripheral nerves (PN) with a collagen-based scaffold, the dermis regeneration template (DRT), has induced regeneration of these organs reliably over several years. An early version of the rationale for treatment of skin loss was reported in 1980 [1]. Results from the first clinical study with 10 massively burned patients were reported soon after [2]. DRT was physicochemically characterized as a natural polymeric network that induces *de novo* synthesis of the dermis, the key tissue in skin that fails to regenerate spontaneously [3]. Seeding of DRT with keratinocytes led to simultaneous regeneration of dermis and epidermis [3]. Even though outcomes were imperfect in these early efforts (e.g., hair and sweat glands were missing), this treatment for extensive skin loss has seen increasing use in the clinic. Increased perfection of outcome, including regeneration of hair follicles and sweat glands, was reported in subsequent studies [4]. Over 340 clinical cases of DRT use are cited in http://www.ncbi.nlm.nih.gov/pubmed/?term=Integra+substitute+skin. An important clinical advantage of induced regeneration has been the absence of morbidity that typically accompanies the replacement of organs by transplantation and other procedures. An example of a clinical result using the commercial version of DRT appears in Fig. 1.

Fig. 1



Regenerated skin in the abdomen of a female. The patient had been deeply burned in the abdominal area which became scarred and lost its compliance. She was treated surgically with excision of the scar to its full depth, followed by grafting with the commercial version (Integra™) of the dermis regeneration template (DRT). Newly regenerated, compliant skin replaced the scarred area. The photo shows the regenerated skin 6 years after the initial surgery (Photo courtesy E. Dantzer, MD, France).

This treatment was later extended to regeneration of peripheral nerves (PN) across long gaps between stumps resulting from transection in animals [5,6]. The relatively recent (2012–2017) elucidation of the regeneration mechanism induced by DRT both at the organ scale and the molecular scale [7–9], summarized below, provides strong motivation for studies that extend the methodology to organs other than skin and PN.

In this review we summarize the salient features of induced regeneration of skin and peripheral nerves as currently understood. A dominant element of this approach stems from the realization that a carefully standardized wound in the injured or diseased organ, together with an appropriate scaffold, provides almost everything that is required to regenerate skin and peripheral nerves.

Why use a wound as a bioreactor to regenerate organs?

Experimental studies of regeneration of skin and PN with animals, as well as in clinical studies, have been based on use of a wound as the site for grafting a collagen-based scaffold. In clinical practice such wounds have typically resulted from accidental trauma. Increasingly, however, surgical procedures are currently being developed, designed to *generate* a wound in the intact organ that is later grafted with DRT. This elective procedure has been used to regenerate the diseased or congenitally abnormal organ, rather than an organ that has been traumatically devastated [10–13]. This development potentially increases the range for future use of a regenerative treatment to terminally diseased organs.

Although a great deal is known about the biochemistry of normal wound healing, many critical details of cell signaling events inside a wound are not yet known and cannot therefore be rationally manipulated to achieve desired clinical objectives, such as acceleration of healing or regeneration. The discovery of a regeneratively active scaffold (DRT) helps to bypass such uncertainty by inducing a benign but decisive modification of the normal wound healing process. DRT short-circuits the natural cell signaling processes during wound healing and results in an important modification of natural healing that yields physiologic tissue rather than scar. This is a result of major medical interest.

An experimental wound suitable for study of induced regeneration not only yields reproducible results from one animal to the next but also provides an accurate answer concerning the incidence or absence of a regenerative outcome. Among different types of tissue in organs [14] the stroma (connective tissue) is the singular tissue which does not regenerate spontaneously following severe injury. It follows that the most important characteristic of an experimental wound that is suitable for a screening study is that it is scrupulously free of stroma [15]. Examples of such wounds are the full-thickness skin wound, grafted with a sheet of the experimental biomaterial; and the completely transected peripheral nerve treated with the two nerve stumps placed inside a tube fabricated from the material being screened for its potential ability to regenerate [15].

The end state of the wound healing process is wound closure, a very useful reference state for organizing information that applies directly to regeneration. Wounds in skin and PN close by a combination of three processes: contraction of wound edges, scar formation and regeneration. Each of these processes of wound closure has been studied quantitatively by several authors [15].

Scar formation in skin wounds appears in the form of collagen fibers that are highly oriented in the plane of the skin wound [16–20]. In PN, collagen fibers of neural scar are arranged circumferentially around each stump [6,21]. Regenerated tissues in skin [22,23] and PN [5,6] have been definitively distinguished from scar. The macroscopic contraction force to close a wound in the rodent skin has been measured at 0.1 N [24]. The contraction force is generated by contractile cells (myofibroblasts, MFB) [25,26] that have themselves been oriented in the plane of skin by the contractile