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Historical background of regenerative medicine and tissue engineering

A regenerációs medicína és a szövetmérnökség történelmi háttere

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Abstract

The ancient desires of men there were emerging from time to time in the tales of many nations and are emerging actually in the sreenplays of the film industry. Flying, travelling in space, visiting other planets, achieving the eternal youth, becoming invulnerable or even the desire for quick recovery are deeply rooted in men's fantasies and some of them are turning out step-by-step as a day-to-day reality.
Regenerative medicine and tissue engineering are interdisciplinary fields of research that utilize the knowledge of engineers, scientists, and physicians to create tissue-like implants. In the most intensive research on tissue regeneration, there are taken cell samples of the patients' relevant tissues, which after multiplication on a host artificial matrix are finally replaced to the damaged area for local regeneration. Henceforward, the regenerated tissue regains its original structure and function. The past four decades witnessed the rapid development of these fields, from laboratory experiments throughs animal testing and clinical trials to the administered therapies. Studying the history of original and novel ideas on this field is a key issue in understanding the latest achievements while appreciating the actual results and the future trends respectively.
This study outlines a brief summary of the background the early history and the present challenges of regenerative medicine.
In this study, I present a brief survey on the background of regenerative medicine and the principles of tissue engineering, followed by discussing the early years of these fields. In the end, I will describe the most relevant questions and scientific challenges that are still to be answered and overcome.

Kulcsszavak: regeneratív medicína, szövetmérnökség, történelem

Keywords: regenerative medicine, tissue engineering, history

Introduction

The past four decades have seen the fast-flowing development of regenerative medicine and tissue engineering, in which research and clinical application focus on treatments to initiate regeneration, replacement, or the repair of aged, diseased, or injured cells or tissues (Vacanti/Langer 1993). These two research areas are interdisciplinary fields of research that utilize the knowledge of engineers, scientists, and physicians to create biological substitutes that can mimic tissues (Polykandriotis et al. 2010).
There are three major approaches in the field of tissue engineering (Kuo/Tuan 2003):

1. Implanting a scaffold to the damaged area, and the cells in the surrounding area can migrate in and populate the scaffold.

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2. Injecting cells from an autologous (from the same individual), allogeneic (from separate individuals of the same species), or xenogeneic (from different species) source.
3. Cell seeded in combination with growth factors on biodegradable scaffolds designed to function as an artificial extracellular matrix, as schematically presented in Figure 1. With time, the scaffold degrades, and the cells simultaneously synthesize a new extracellular matrix and produce a functioning tissue.

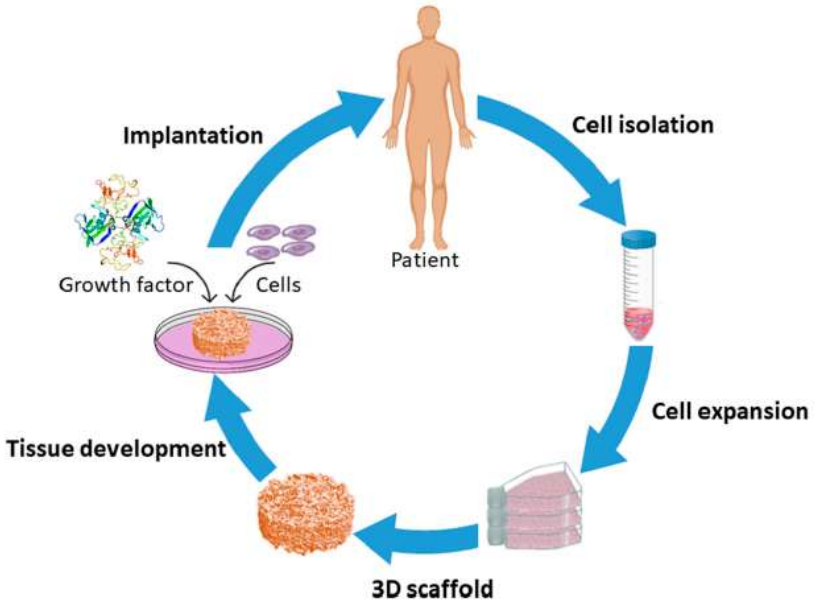

Figure 1. Schematic of the tissue engineering approach, where cells are introduced to the scaffold (Asadian et al. 2020). The main goal of implantation is to induce regeneration in the damaged tissue and restore its original function.

The short story of tissue engineering

In Greek mythology, the great Titan Prometheus stole fire from the gods and gave it to humanity as the symbol of civilization and technology. Zeus sentenced him to eternal torment, chaining him to a rock and having an eagle peck out his liver, which would grow back overnight (Figure 2.). Regrowing his liver every day for 30 000 years made him the icon of regenerative medicine (Aeschylus n.d.). Repairing injured, diseased, or even completely missing tissues appeared in both scientific works and myths. The first known detailed description of the limb regeneration of amphibians was written by Aristotle (Barnes 2014); in the legend of Saint Damian and Cosmas (Voragine 1275), a leg of a patient was transplanted and healed. The dream of regenerating tissues and organs infinitely is an ancient desire of mankind, which has been pursued since the prehistorical ages.

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Figure 2. Prometheus, the symbol of regenerative medicine

One of the first significant findings of modern history regarding tissue engineering was the scientific achievement of Alexis Carrel. He set the groundwork for cell culturing in 1912 by taking cells from a chicken embryo and growing them for more than 30 years (Hamilton 2016). The first clinical use of cell therapy was replacing tissues via transplantation. In 1869, the first successful skin transplant was performed by Jacques-Louis Reverdin, who used donor skin from a different site on the same individual's body. In the middle of the 20th century, transplant medicine went through accelerated development. The first kidney transplant occurred in 1954 between two identical twins in Boston (Hakim et al. 2003), followed by the first lung and liver transplants in 1963 (Calne 2003) and the first heart transplant in 1967 (Lewis 2012). While transplant medicine made rapid progress and has an undoubted impact on people's lives, the main restraint of its application is the limited number of suitable transplant donors.

The first engineered tissue-based therapies were applied for skin replacement, because of its relatively low risk (compared to heart and kidney), and the fact that this tissue does not require extensive vascularization. The standard treatment for deep cutaneous wounds remained autologous skin grafts, using donor sites from the patient remaining to harvest skin graft material (Papini 2004). To cover larger areas of the wound, it is possible to create a uniformly perforated skin graft mesh. However, this method may result in limitations of mobility caused by graft construction and a crocodile skin-like appearance of the scar (Berthiaume et al. 2011). If the patient did not have enough available skin remained, xenografts from various animals were implanted – accompanied by the risks of rejection and infections (Halim et al. 2010). These limitations brought artificial skin substitutes into being. The history of the first tissue-engineered products started in the four Massachusetts laboratories of Bell, Green, Yannas, and Vacanti. These research groups followed different strategies and developed approved medical products from their skin grafts.

In 1975, Howard Green and James G. Rheinwald at Harvard Medical School described the technique in vitro culture skin epidermis, starting with single cells harvested from the patient (Rheinwhald/Green 1975). In 1983, using small patches of skin removed from two (5 and 7 years old) burn victims who had suffered third-degree burns over 97 percent of their bodies, the laboratory-grown substituent grafted onto their bodies helped to save their lives (Roberts 2015). Based on the technology developed by Green, the first cell-based tissue-engineered product used in living cell therapy was commercialized as Epicel (Green et al. 1979; O'Connor et al. 1981; Rheinwatd/Green 1975).

In the 1980s, Eugene Bell and his colleagues at the Massachusetts Institute for Technology developed skin equivalents to reconstruct both the dermis and epidermis. This composite skin product was first made by

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seeding dermal and epidermal skin cells on collagen gels (Bell et al. 1981). This technique uses allogeneic cells isolated from the neonatal human foreskin and functions like a wound stimulant that will be rejected by the patient. These substitutes are applied for the treatment of recalcitrant venous leg ulcers and diabetic foot ulcers. Based on this technology, in 1998, the first US FDA (Food and Drug Administration) approved allogeneic tissue-engineered product for clinical use was commercialized as Apligraf (Figure 3.), marketed by Organogenesis (Canton, MA).

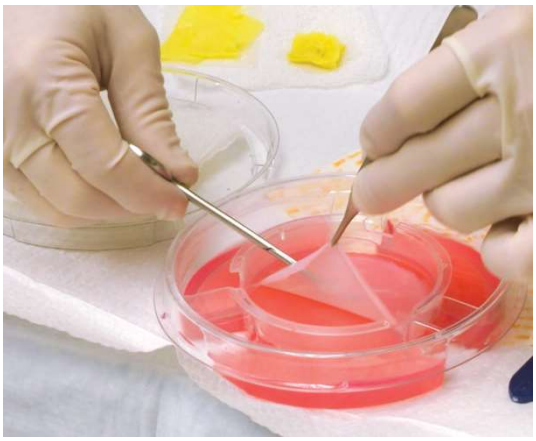

Figure 3. Apligraf ®, a composite skin product before use (apligraf.com)

Yannas and Burke developed protein-based acellular scaffolds that could support the growth of dermal fibroblasts and regenerate damaged tissue, especially in burn wounds. Based on the findings of their research group, a dermal regeneration template consisting of collagen and glycosaminoglycan was produced and commercialized as Integra (Yannas et al. 1982). Designing biocompatible materials that can host cells and contribute to their adhesion and proliferation is one of the most challenging tasks in material science.
The work of J. G. Vacanti and Langer focused on the construction of artificial scaffolds for cell culture (Vacanti/Langer 1993). Instead of copying the biological structures using natural substances, they used biocompatible synthetic matrices that had better reproducibility and lower costs. Employing polymer sciences, the research group was able to manipulate the chemical structure of the scaffold and earned desirable mechanical and biological properties (Vacanti/Langer 1993), (Vacanti 1988). In 1996, C. Vacanti and his team created a scaffold from a synthetic nonwoven mesh of poly(glycolic acid) and shaped it into the form of a human ear. To create a cartilage structure, the implants were seeded with chondrocytes and implanted under the skin of a mouse. The auriculosaurus, also known as the earmouse induced considerable media hype and unrealistic extrapolations of tissue engineering (Cao et al. 1997).

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Figure 4. An ear-shaped scaffold implanted under the skin of a mouse. (Wikipedia, 1 April 2021)

Tissue engineering received widespread media publicity, yielded high expectations, and also unhelpful background noises. This early success in regenerating tissues spawned a great deal of enthusiasm, yet resulted in scientific overclaim. In 2000, Time magazine identified tissue engineer as 'The Hottest Job' (the hottest career option) for the future, and it was predicted that body parts would be grown in Petri dishes (Rawe 2000), (Kratz/Huss 2003). However, such treatments turned out to be far more difficult when it came to their real-life application. Due to the enormous time pressure from the media, the initial schemes for tissue engineering were oversimplified, and the first medical products did not behave as originally intended (Kemp 2006). In the last two decades, with the incorporation of advances in molecular and cellular biology and the tools of nanotechnology and engineering, several technologies have been developed and may facilitate future breakthroughs (Berthiaume et al. 2011). Nevertheless, tissue-engineered medical products still have not reached mainstream bedside utilization (Mao/Mooney 2015), (O'Donnell et al. 2019).

Scientific challenges remain

Despite the early success with skin and cartilage, there are only a few examples of human application to date. The work of multiple research groups improves our scientific understanding of the countless factors taking part in the complex processes of regeneration.

One of the most significant challenges is associated with the 'scale-up' of cell-based products, that is, to design complex organs in a clinically relevant size, a large number of cells are needed to generate the required tissue. The utilized cells are usually derived from donor tissue or stem cells. These cell-based products require long cultivation procedures due to the limited amount of supply (Vacanti 2006). Furthermore, these areas require extensive vascularization to avoid creating a hypoxic environment after implantation. To compensate for the lack of preexisting vascular network, scaffolds were designed to promote a rapid vascular ingrowth of endothelial cells, with the ability to print the desired cell type in precise layers in a thermoreversible gel (Wilson/Boland 2003), (Boland et al. 2003).

Another key scientific hurdle is graft rejection. The immune rejection of a biocompatible cell-free product is unlikely, but the cell-based ones may trigger a strong immune response (O'Donnell et al. 2019). The product that is genetically identical to the patient reduces immunogenicity and holds the promise of reducing rejection (Solez et al. 2018). From another perspective, the patient can also be made more graft-tolerant through immunosuppression.

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Designing scaffolds have also remained challenging. In native tissue, the extracellular matrix is the extensive three-dimensional network that provides structural support to the surrounding cells. To allow the cells to function as they would do natively and to provide the proper chemical milieu and the mechanical properties, scientists are creating an artificial extracellular matrix, which cells can adhere to and proliferate on. These scaffolds have to support cell attachment, the adequate diffusion of nutrients, provide the mechanical rigidity or flexibility, and need to fulfill many requirements regarding reproducibility, biocompatibility, and biodegradability (Berthiaume et al. 2011). Tissue-engineered medical products are met with hesitation from the surgeon if they pose an alternative from the traditional approach, require uncomfortable or non-standard delivery mechanism, or require more operating time (O'Donnell et al. 2019), (Dlaska et al. 2015). These products have to be straightforward, ergonomic and be pragmatically integrated into the operation workflow (Hollister/Murphy 2011).

The road from these excellent scientific ideas to mainstream clinical application is much longer and more difficult than the enthusiasts originally predicted. It is a complex, multidisciplinary field of medicine, requiring a deep understanding of the process of regenerating tissues. With that in hand, we will be able to take the inherent challenges of tissue engineering.

Summary
The field of regenerative medicine developed rapidly in the last four decades. Based on the results of four Massachusetts laboratories, the ancient human desire to regenerate our aged and injured body appeared more attainable than ever before. These early successes fueled a lot of enthusiasm, resulting in unrealistic extrapolations about the bedside application of the method. The objectives were transformed from the high expectations of 'growing organs in a Petri dish' to more realistic goals. Today, a handful of research groups around the world are working on creating tissues of the heart, and with time, replacing coronary arteries and heart valves will become more and more realistic in future mainstream clinic applications. At the moment, tissue-engineered medical products are not widely adopted in clinical practice. Significant challenges remain unanswered, but the optimism for potential solutions and that regenerative medicine will have a real and positive impact on people's lives is very high.

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