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Review

Scientific principles of regenerative medicine and their application in the female reproductive system

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ABSTRACT

The goal of regenerative medicine is to repair, replace, or regenerate diseased tissues/organs in order to restore normal function. In this paper we will first discuss the general principle of regenerative medicine and the various techniques and approaches that have been used to replace or regenerate cells in diseased tissues and organs. Then, we will review different regenerative medicine approaches that have been used to treat specific diseased tissues and organs of the reproductive system in both animal and human experiments. It is clear from this article that regenerative medicine holds significant promise, and we hope that the review will serve as a platform for further development of regenerative medicine technologies for the treatment of inadequacies of the reproductive system.

Contents

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1. Introduction

Regenerative medicine represents a field in the health sciences that aims to repair, replace or regenerate human cells, tissues, or organs in order to restore normal function [1]. The field of regenerative medicine encompasses various technologies that range from tissue engineering to cloning, as illustrated in Fig. 1. Tissue engineering combines the principles of cell transplantation, material science, and bioengineering to develop new biological substitutes that may restore and maintain normal organ function. Tissue engineering strategies generally fall into two categories: (i) the use of acellular matrices, which serve as guides for proper orientation and direction of new tissue growth but depend on the body's natural ability to regenerate, and (ii) the use of the matrices seeded with cells. Acellular tissue matrices are usually prepared by manufacturing artificial scaffolds, or by removing cellular components from tissues via mechanical and chemical manipulation to produce collagen-rich matrices [2,3]. These matrices tend to slowly degrade after implantation and are generally replaced by the extracellular matrix proteins that are secreted by host cells that infiltrate the initial matrix implant.

Cells can also be used for therapy via injection, either with a carrier such as a hydrogel, or alone. In addition cells can be used for matrix-based tissue engineering strategies. For this purpose, a small piece of donor tissue is dissociated into individual cells. The cells are either implanted directly into the host, or they are expanded in culture, attached to a support matrix, and then the cell-matrix construct is implanted into the host. The source of donor tissue can be heterologous (xenogeneic source such as bovine), allogeneic (same species, different individual), or autologous. Ideally, both structural and functional tissue replacement will occur with minimal complications. Autologous cells derived from a biopsy of tissue are the preferred type to use. They are obtained from the host, dissociated from the tissue biopsy, and expanded in culture. Next, they are implanted back into the same host. The use of autologous cells, while it may cause an initial inflammatory response, avoids rejection, and thus the deleterious side effects of immunosuppressant medications can be avoided. Thus, most current strategies for tissue engineering depend upon a sample of normal autologous cells from the diseased organ of the host.

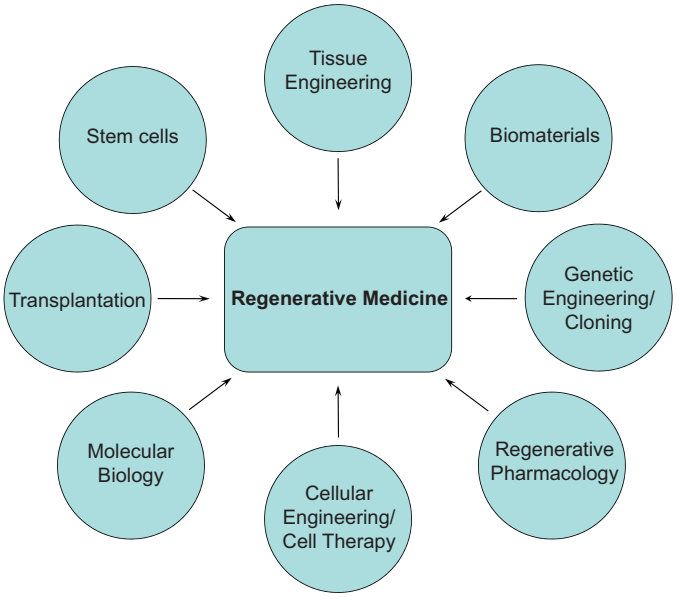

Fig. 1. Schematic representation of the various components of regenerative medicine.

However, for many patients with extensive end-stage organ failure, a tissue biopsy may not yield enough normal cells for expansion and transplantation. In other instances primary autologous human cells cannot be expanded from a particular organ such as the pancreas. In such situations, stem cells are in vision as being an alternative source of cells from which the desired tissue can be derived. Stem cells can be derived from discarded human embryos (human embryonic stem cells), from fetal tissue, or from adult sources (bone marrow, fat, skin). Therapeutic cloning has also played a role in the development of the field of regenerative medicine. Recently the technology of induced pluripotency in which cells such as fibroblasts are "reprogrammed" to behave like stem cells has been described, and it may also provide a new source of cells for tissue-engineering strategies.

2. Biomaterials for use in tissue engineering

In many cell based tissue engineering methods, cells are obtained from the tissue, expanded *in vitro*, and then seeded onto a scaffold composed of an appropriate biomaterial. The biomaterials replicate the biological and mechanical function of the native extracellular matrix (ECM) found in tissues in the body by serving as an artificial ECM. Biomaterials also provide a three-dimensional scaffold for the cells to adhere to and form new tissues with appropriate structure and function. They also allow for the delivery of cells and appropriate bioactive factors to desired sites in the body. Bioactive factors, such as cell-adhesion peptide and growth factors, can be loaded along the cells to help regulate cellular function. As the majority of mammalian cell types are anchorage dependent and will die if no cell-adhesion substrate is available, biomaterials provide cell-adhesion substrate that can deliver cells to specific sites in the body with high loading efficiency. Biomaterials can also provide mechanical support against *in vivo* forces and ensure that the predefined three-dimensional structure of an organ is maintained during tissue development.

The ideal biomaterial should be biodegradable and bioresorbable to support the placement of normal tissue without inducing inflammation. Incompatible materials that induce inflammatory or foreign body response eventually lead to cellular/tissue necrosis and/or rejection. Degradation products, if produced, should be removed from the body via metabolic pathways at an adequate rate to keep the concentration of these products in the tissues at a tolerable level [4]. The biomaterial should also provide an environment in which appropriate regulation of cell behavior (adhesion, proliferation, migration, and differentiation) can occur such that functional tissue can form. Cell behavior in the newly formed tissue has been shown to be regulated by multiple interactions of the cells with the microenvironment, including interactions with cell adhesion ligands [5] and with soluble growth factors. Since biomaterials provide temporary mechanical support while the cells undergo spatial reorganization into tissue, the properly chosen biomaterials should allow the engineered tissue to maintain sufficient mechanical integrity to support itself in early development, while in late development, it should begin to degrade so that it does not hinder further tissue growth [6].

Current biomaterials aim to mimic the role of natural extracellular matrix (ECM), which can support cell adhesion, differentiation and proliferation. ECM-mimicking biomaterial scaffolds need to be designed considering the following requirements. First, suitable biomaterials must be selected for particular applications [7–9]. Second, biomaterial scaffolds require a highly open porous structure with good interconnectivity, yet possessing sufficient mechanical strength for cellular in- or outgrowth [10]. Third, the surface of the fabricated scaffolds must be able to support cellular attachments, proliferation and differentiation [11–13]. Fourth, drug or