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Regenerative medicine for the treatment of reproductive system disorders: Current and potential options ☆

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ABSTRACT

Regenerative medicine has opened new avenues for treating patients with severe reproductive system disorders, such as congenital abnormalities, cancer, trauma, infection, inflammation and iatrogenic injuries. Over the past two decades, scientists have advanced the field of reproductive tissue engineering to restore normal sexual function and preserve fertility in both female and male patients. In this review, we summarize recent advances in the use of cell, tissue, and organ-based regenerative medicine strategies for clinical application in reproductive system disorders.

Contents

1. Introduction

For many years, hormonal and surgical treatments have been used to help patients suffering from reproductive system disorders. In the 21st century, regenerative medicine has become a promising concept in the development of new therapies for all fields of medicine, including reproduction [1]. The field of regenerative medicine includes several different areas of biomedical technology, including biomaterials, tissue

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engineering and stem cell therapy. Three main strategies have been used for tissue engineering: 1) Use of extracellular matrices (ECM) without cells, allowing the natural ability of the body to generate new tissue; 2) Use of ECM seeded with cells for implantation; 3) Direct injection of cells either with or without carriers such as hydrogels (Fig. 1). The ECMs used for tissue engineering may either be synthetic, or derived from natural tissues [2,3]. A variety of different cell types may also be used, including: 1) Tissue specific stem cells; 2) Mesenchymal stem cells; and 3) Pluripotent stem cells, such as embryonic stem cells, induce pluripotent stem cells (iPS), or amniotic and placental stem cells. The source of these cells can be either autologous or allogeneic (Fig. 1). Autologous cells derived from a small biopsy are the preferred cell type. The biopsy is obtained from the patient, and the cells isolated from this biopsy tissue are expanded *in vitro*. However, for some patients, this is not possible as there is insufficient functional tissue to obtain a biopsy. Therefore other sources of cells, such as stem cells (either autologous or allogeneic) might be used for these patients [2,3]. The ultimate goal of regenerative medicine strategies for the treatment of reproductive system disorders is to restore normal sexual function and preserve fertility. In this review, we summarize the most recent advances in using cell, tissue, and organ-based regenerative medicine strategies for clinical applications in treating reproductive system disorders.

2. Female reproductive system

2.1. Vagina

Vaginal agenesis is a genital tract anomaly that occurs in 1 out of 5000 females [4]. Congenital vagina malformations such as Mayer–Rokitansky–Kuester–Hauser (MRKH) syndrome, cloacal malformation, or thick transverse vaginal septum can adversely affect vaginal anatomy and consequently result in sexual dysfunction [5]. Extensive surgery in the pelvis due to cancer, severe trauma, or transgender operations can also create the need for vaginal reconstruction [6–8]. A recent systematic review of optimal management of isolated vaginal agenesis due to MRKH or androgen insensitivity syndrome (AIS) showed that the existing data in the literature is not consistent [9] However, overall data of 7 different vaginoplasty techniques revealed that the conservative method of using dilation had the fewest complications, with success rates ranging between 43% and 94.5%, with an average vaginal length of 6.65 cm [9]. If dilation fails or the defect is large, surgical vaginoplasty methods are required. The main challenge is the lack of sufficient native tissue to reconstruct the vagina. The feasibility of tissue engineering of vaginal organ was investigated using rabbit cells [10]. Rabbit vaginal epithelial and smooth muscle cells (SMC) were expanded *in vitro* and seeded on polyglycolic acid (PGA) scaffolds at a density of 10–20 million cells/cm^2 [10]. The seeded scaffolds were then implanted subcutaneously in nude mice. Evaluation of implants by immunohistochemistry, Western blot and organ bath electrical stimulation after 6 weeks revealed formation of tissue that was phenotypically and functionally similar to native vagina [10]. In another study, radiographic analysis of neovagina in rabbits six months after total vaginal replacement, demonstrated wide, patent vaginal structures, without strictures [7].

Several materials have now been used to engineer vaginal tissue, including amniotic membrane [11], oxidized cellulose [12], peritoneum [13], small intestinal submucosa [14], autologous buccal mucosa [15] and autologous *in vitro* cultured tissue [16]. A 28 year old patient with MRKH syndrome had a 1 cm^2 full-thickness mucosal biopsy taken from the vaginal vestibule. Cells were isolated from the sample,

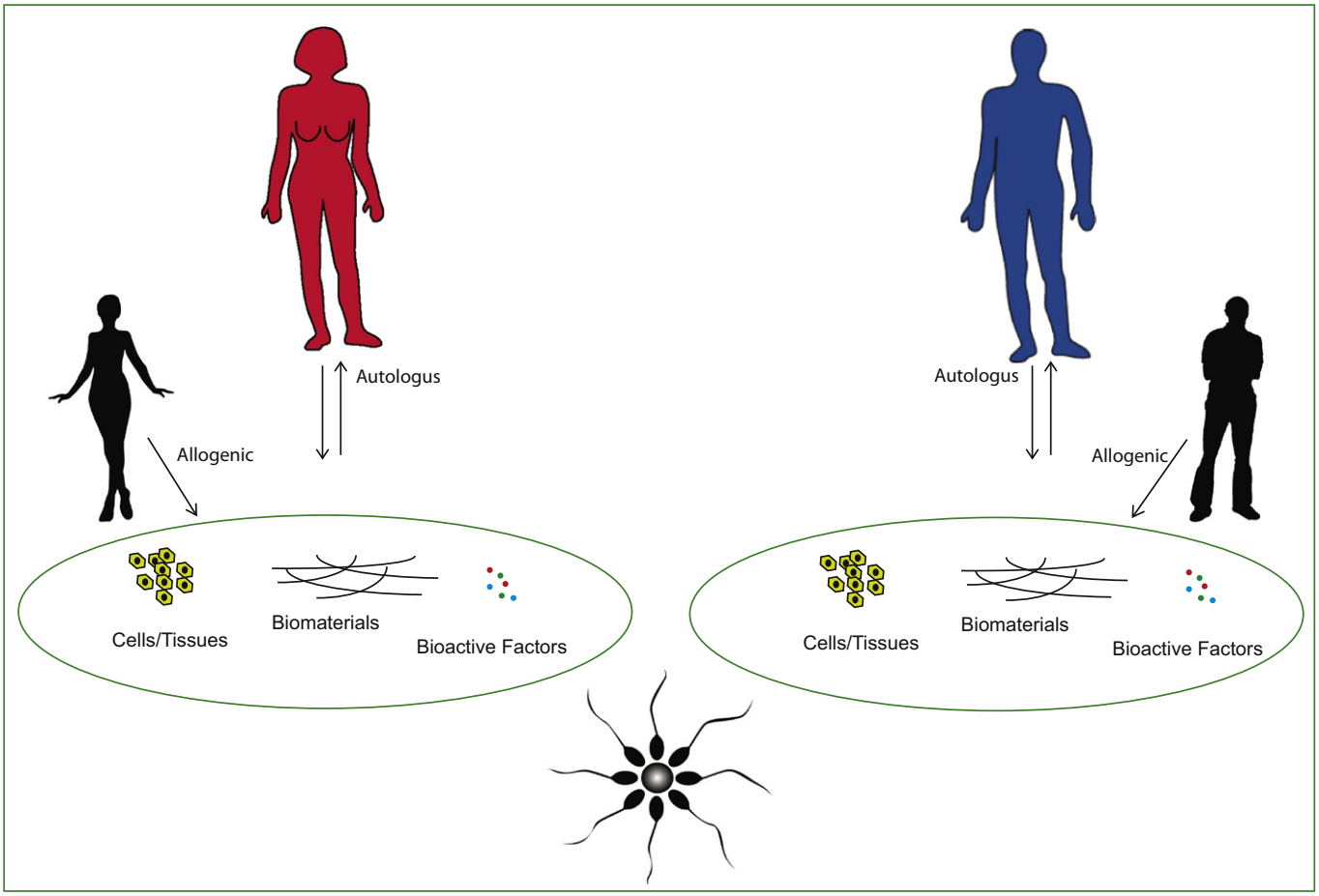

Fig. 1. Schematic diagram showing the application of autologous or allogeneic tissue based therapies for the treatment of male and female reproductive system disorders.