Featured Article

Stem cell and tissue engineering in breast reconstruction

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Abstract: Breast cancer worldwide is the most common cancer in women with incidence rate varying from geographic areas. Guidelines for management of breast cancer have been largely established and widely used. Mastectomy is one of the surgical procedures used treating breast cancer. Optionally, after mastectomy, appropriately selected patients could undergo breast reconstruction to create their breast contour. Many techniques have been used for breast reconstructive surgery, mainly implant-based and autologous tissue reconstruction. Even with highly-experienced surgeon and good-quality breast and autologous substitute tissue, still there could be unfilled defect after mastectomy with reconstruction. Stem cell, in particular, adipose-derived stem cell residing within fat tissue, could be used to fill the imperfection providing optimal breast shape and natural feeling of fat tissue. However, whether surgical reconstruction alone or in combination with stem cell and tissue engineering approach be used, the ultimate outcomes are patient safety first and satisfaction second.

Keywords: Stem cell; adipose-derived stem cell; tissue engineering; breast reconstruction

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Introduction

Breast cancer is the most common form of female cancers, accounting for approximately 30 percent of all cancerous case in women. There were 1.4 million new cases of breast cancer amongst women worldwide, an increase of 4% over ten years (1,2). With advanced technological development in screening, detection, and treatment of breast cancer, survival rate has been continuously increasing with a current 5-year survival rate at nearly 90% in the United States (3). Approximately 40 percent of patients will undergo mastectomy as part of the surgical treatment for their breast cancer (4,5). By increased improvement in early detection and survival, mastectomy is considered more to have a negative impact on body image together with sexual function with longer life. Breast reconstruction following mastectomy for breast cancer is currently an optional treatment which helps women to recover from the physical and psychological emotion of breast cancer management. A systematic review presented that international breast reconstruction rates ranged widely from 4.9% to 81.2% among different countries (6). Rates of breast reconstruction in the United States and United Kingdom are estimated around 25% which is gradually mounting (7). Breast reconstruction may be performed as a simultaneous or delayed procedure, using breast implants, autologous tissue or a combination of the two. Cell-based approach and tissue engineering also play an advantageous role in breast reconstruction, particularly in the context of increased breast circumference and improved natural sensation of the outcomes of breast reconstruction. Conventional fat grafting or cell-assisted lipotransfer method mainly depends on adipose-derived stem cells resulting in superior and durable outcomes. Tissue engineering in breast reconstruction is not limited solely to cell-based techniques. To use acellular dermal matrix enables surgeon to modify the breast pocket in desired position for the placement of expander or permanent implant leading to optimal breast contour and patient satisfaction. In this review, stem cells principles and tissue engineering will be discussed. Furthermore, the potential benefits of these cells and tissue-constructed material will be presented. The use of stem

cell and tissue engineering approach in practical breast reconstruction will be explored and elaborated.

Stem cell principles

Cells are the basic structural and functional units in biology. In mammalian development, it begins with the formation of unicellular zygote, which arises from the fertilization process between a sperm and an egg from the paternal and maternal origins respectively. A total of 10^{14} cells have been estimated to reside in the human body, and which can be categorized into approximately 230 specialized cell types according to their functional phenotypes (8). Stem cells are cells which possess an ability to maintain self-renewal or differentiate to any specialized cells. The stemness of every cell type arises from the inner cell mass (ICM) cells of the blastocyst in an embryonic stage (9,10). Later on, these ICM cells give rise to all of different stem cell types or differentiated mature cells, forming tissues and organs. Characteristically, the particular stem cells have a restricted capacity to turn into only specific mature cells which phenotypically characterize the tissue where they reside. For instance, hematopoietic stem cells and epidermal stem cells differentiate into blood cells and skin cells, respectively.

The initial concept of stem cell biology originated from the study back in 1961. James Till and Ernest McCulloch published serendipitous findings proving the existence of stem cells in hematopoietic tissues (11). Subsequent evidence of stem cells in the hematopoietic system has also been demonstrated in peripheral blood and bone marrow (12,13). In addition, clinical experiments also proved the promise of bone marrow transplantation for the treatment of cancer and non-cancer hematopoietic diseases (14,15). Taken all together, these findings in hematopoietic stem cells have led to an opening of the stem cell biology paradigm.

In the basic principle of stem cell, stem cell fates and states are of importance and considered as a core of stem cell biology. Understanding cell-fate decisions in stem cell population is important for translating stem cell biology towards clinical medicine. While much still remain to be understood, the four cell-fate options for stem cell have been described (16), including self-renewal, differentiation and lineage-specification, programmed cell death or apoptosis, and quiescence. Self-renewal is division with maintenance of the undifferentiated state whereas quiescence is the undifferentiated state with no division.

Furthermore, stem cells also undergo changes resulting in loss of stem cell state, either differentiation or death (apoptosis). These cell-fate decisions are regulated by both cell-intrinsic mechanisms and cell-extrinsic signals from the niche, the microenvironment that stem cells populate. In addition, the developmental potency of stem cell can be classified into four categories according to differentiated progeny states, including totipotency, pluripotency, multipotency, and unipotency.

Resources of stem cells

Resources of stem cells come from many sources in humans. They are categorized as adult stem cells, umbilical cord blood stem cells, embryonic germ cells, and embryonic stem cells. Besides, recently, reprogrammed stem cells and partially reprogrammed cells have also been created and identified. Briefly, adult stem cells or somatic stem cells populate, proliferate and generate differentiated offspring in a tissue or organ (17). Adult stem cell population in human body has been identified in, for instance, bone marrow, intestine, brain, epidermis, hair follicles and adipose tissue. They are able to divide and differentiate into mature cells when needed in a particular tissue.

Human embryonic stem (ES) cells

In the past decades, one key scientific discovery was the derivation of mouse and human embryonic stem cells. Evidence has shown that these ES cells could be manipulated to generate various cell types from all three germ layers *in vitro* and *in vivo*. Since the discovery of mouse ES cells in 1981 by two independent research groups (9,10), great attention from scientists has been focused towards insights into the biology of stem cell development. The consequent intellectual skeleton of human ES cell biology was originated and enabled from the comprehension and conception of mouse ES cells. In 1998, James Thomson and colleagues published the first derivation of human ES cells from human blastocysts (18). The established human ES cell lines expressed cell surface markers which characterized undifferentiated cells, including stage-specific embryonic antigen (SSEA)-3, SSEA-4, TRA-1-60, TRA-1-81, and alkaline phosphatase. In sum, these ES cell lines should hold gigantic promise in studying human developmental biology, drug discovery, transplantation, and regenerative medicine. The derivation of pluripotent human ES cells has opened new exciting paradigm for stem cell biology; however, there were still concerns about potential risks,

such as uncontrolled or misdirected growth, and ethical controversy associated with the source of human ES cells.

Following the characterization of first human ES cell lines in 1998, standard protocols have been steadily developed towards clinical-grade applications, including maintenance of these cells under animal-derived-free and defined culture components (19,20). Moreover, essential protocols for induced differentiation processes of human ES cells into various differentiated cell lineages such as neurons, keratinocytes, and cardiomyocytes have been largely optimized (21-23). In addition, by integrating with an engineering approach, several of these envisioned applications of ES cells would require production of high number of stem cells and their derivatives in a scalable process, effective automated bioprocessing systems are required to achieve a large-scale production and to reduce the amount of associated labor energy and time (24,25). Preclinical studies in animals have proved that derivatives of differentiated human ES cells could provide functional replacements in diseased tissues, typically marked by loss of cells, such as for Parkinson's disease, macular degeneration and cardiac insufficiency following infarction (26-28), and clinical trials have been approved for cellular therapy in humans for macular degenerative disease (29). Despite the promise of ES cells in regenerative medicine, there are essentially two major risks of immunogenicity and tumorigenicity which are potentially associated with clinical uses of ES cells. Besides these biological concerns, controversy about ethical issues of using human ES cells has been broadly debated (30).

Induced pluripotent stem cells

In 2006, Yamanaka astonished the world by demonstrating that transcription factor-induced cell reprogramming was achievable in somatic cells (31). The enforced expression of four key transcription factors, Oct4, Sox2, Klf4, and c-Myc, could reprogram mouse fibroblasts to pluripotent states. These reprogrammed pluripotent cells expressed similar characteristics to ES cells and obtain comparable developmental potential as ES cells. "Induced Pluripotent Stem Cells or iPSCs" was first used to describe these reprogrammed cells. Subsequently, a year later, first human reprogrammed pluripotent stem cells were successfully generated from human fibroblasts by two research groups (32,33). Yamanaka's team successfully transformed human fibroblasts into iPSCs using the same four pivotal genes, *OCT4*, *SOX2*, *KLF4*, and *c-MYC*, with a retroviral-mediated transfection system whereas another team, led by Thomson, used different combination of genes, *OCT4*, *SOX2*, *NANOG*, and *LIN28*, with lentiviral system for cell reprogramming. The observation from these two independent results indicated that Oct4 and Sox2 were core transcription factors in common and might not be dispensable for human iPSC reprogramming. This phenomenal generation of iPSC has created the possibility that human iPSCs might provide the same therapeutic potential as human ES cells without ethical dilemma of using human embryos. Since this first establishment of human iPSCs, enormous scientific discoveries and techniques have been described to facilitate both mechanistic insights and translational studies of iPSCs for clinical settings.

Over the past seven years, various reports on generating iPSCs with a reduction in genetic manipulation and genome-integrating viruses with more efficiency have been described (34-36). In addition, microRNAs recently have been effectively applied for iPSC production without any required exogenous transcription factors (37,38). Differentiation protocols for iPSCs into specific lineages have been established (39-41). Moreover, because these iPSCs can be derived from patient's own cells, they give researchers the ability to model human diseases and to promise a new framework in drug development in an unprecedented manner (42-44). The proof-of-concept in which iPSC technology can be used for the generation of disease-corrected and patient-specific cells with potential value for cell therapy applications has also been demonstrated (45,46). Patient-own iPSCs pose a reduced risk of immunological rejection and result in an avoidance of ethical dilemmas. Several concerns of iPSCs need to be addressed before patient-specific iPSCs can advance into the clinic. For instance, a single reprogramming experiment usually generates multiple iPS cell lines which are not always identical or even not fully reprogrammed iPSCs (47). Each individual iPS cell line needs to be fully characterized with reliable standard protocol to identify bona fide iPSCs and to ensure pluripotency capacity and safety. Another risk of iPSCs when applying iPSC treatment to human subject is tumorigenicity. This problem also exists in human ES cell transplantation. Furthermore, genetic and epigenetic instability of iPSCs (48-50) must be considered. Thus, the justification of safety for the use of pluripotent stem cell or reprogrammed pluripotent stem cell is of utmost importance in clinical settings.

Adipose-derived stem cells (ADSCs)

Adipose-derived stem cells are characterized as one type of somatic stem cells which reside in adipose tissue. Although absolute characteristics of these cells still remain questionable, they indeed contain multipotent property (51). ADSCs could be applied in regenerative medicine in various conditions. They can differentiate into adipocytes, osteoblasts, chondrocytes, myocytes and neurons under specific ingredients and conditions (52). Adipose tissue represents an abundant and accessible source of ADSCs which are one of the most promising stem cell types. ADSCs are not only easy to recover but also stable to large-scale expand. The large volume of adipose tissue obtained from a liposuction procedure in combination with the relatively high frequency of ADSC results in substantial stem cell sources. There were also attempts to derive adipocyte from inducing differentiation from ES cells and iPSCs (53,54). However, the protocols to obtain the induced cells have not provided a homogenous population of adipocytes. Together with the large resource and easy access of adipose tissue, the differentiation of ES cells and iPSCs into adipocytes or adipose stem cells seems unnecessary. Methods for the isolation and expansion of ADSCs have been established and well-described (55). Regarding their multipotent property, concern remains regarding the potential risk of tumorigenicity in ADSCs. Until now, there has been no report, statistically significant, presenting neoplastic occurrence when using ADSCs.

Tissue engineering

Tissue and organ contain complex characteristics. It is obvious that in order to understand tissue and organ level performance, complex cellular and intracellular control mechanisms must be profoundly comprehended. With innovative tools in genetic, molecular, cellular, and printing technology, the relevance of designed structure and function combined with bioartificial fabrication is possible (56,57). The purpose is to construct the biological substitutes that can resemble tissues for diagnostics and can replace diseased or damaged tissues. A great portion of this successful approach has been demonstrated in constructed skin and cartilage components (58,59). *In vivo*, stem cells reside in a complex microenvironment characterized by their local geometry, by specific types of surrounding cells and ECM components. Their cell-cell and cell-ECM interactions are vital for stem cell intra- and inter-cellular signaling mechanisms. Growth factors are a particular group of proteins that play major signaling ingredients to activate proliferation and differentiation pathways. Novel material used in tissue engineering scaffolds has been introduced such as recombinant proteins and synthetic polypeptides (60). In addition, scaffold-free production techniques have been developed for potential use in regenerative medicine, solely based on cell-based and cell-aggregated engineered tissues. The recent developed scaffolds are smart in several ways; however, *in vivo* environment creates dynamic changes and, thus, temporal control over the process is still hardly to be monitored and maintained.

Clinical use of stem cell and tissue engineering in breast reconstruction

ADSCs have been widely used in breast reconstruction, commonly named as lipofilling or lipotransfer or fat-grafting method. This conventional technique has been shown beneficial in both implant-based and autologous breast reconstruction (61), mainly on cosmetically breast contour and emotionally natural sensation of reconstructive breast. One of paramount concerns for fat-grafting is potential associated risk of ADSCs with tumor seed activation and neoplastic formation. Theoretically, ADSCs could potentiate cancer risk or recurrence from endocrine, paracrine, and autocrine effects, stimulating angiogenesis and cell proliferation. Nevertheless, thus far, no clinical evidence supports a higher risk of tumor recurrence and cancer formation in lipotransfer patients (62). Even with higher relative proportion of ADSCs in cell-assisted lipotransfer (CAL) method (63), rates of local tumor recurrence and metastatic cancer remain unchanged. On the contrary, CAL might result in more durable outcomes and less cancer recurrence than conventional fat transfer (63). More prospective clinical data should be monitored and warranted to determine whether lipofilling is dangerous and potentially increases cancerous recurrence in patients. More importantly, performing autologous fat grafting can lead to major complications such as sever breast infection requiring emergent corrective operation. Therefore, should only well-trained surgeons perform this procedure. One interesting unpublished data showed that more fat necrosis and breast complication occurred in old-age group patients. One possible theory could be a reduction of ADSCs in fat tissues. This assumption still requires justification whether it is, in fact, true.

Acellular dermal matrix (ADM) is a tissue scaffold

providing additional tissue support and minimizing rippling and wrinkling of breast contour (64). In two-stage expander and implant reconstruction, ADM provides similar safety but less need for manipulation of the prosthetic comparing to conventional technique. In future, many developing advanced materials together with superior scaffold fabrication technique will offer more suitable and easy-to-use substitutes with improved patient outcomes.

Stem cell and tissue engineering approach is a promising field in breast reconstructive surgery. To understand the basic biology of stem cell is an important step in cell-based and tissue-constructed therapy for patients with breast reconstruction. Further challenges are how we can reduce the complications, avoid tumor recurrence, and increase patient satisfaction with state-of-the-art stem cell and tissue engineering paradigm for breast reconstructive surgery.

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