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Stem Cell Research: A New Era for Reconstructive Surgery

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1. Introduction

Reconstructive Surgery has gained tremendous development due to the emergence of flap techniques, since last century. However, many defects and deformities still cannot be cured satisfactorily, such as severe facial defects, or deformity caused by burns, tumor resection, or trauma. It can be more complicated if the injury involves the loss of bone or cartilage. The allotransplantation of composite tissue has been used for such cases, however, such technique is limited in a lack of source of tissue, complicated surgical process, and severe morbidity left at the donor site. Composite tissue allotransplantation is also regarded as one of the possible resolutions. Nevertheless, immunological rejection, lack of proper donors, and more importantly, psychological rejection, making such transplantation difficult to be a common or routine treatment. [1-6]

The exploration of unlimited tissue engineering sources has been considered to be a promising alternative for such cases. Significant advances have been achieved in this area, especially after various adult stem cells have been found to contribute to the regeneration of various tissues in the body. This chapter begins with an introduction of progress of tissue engineering in plastic surgery. Three types of tissues, which are of specific interest in plastic and reconstructive surgery including skin, cartilage and bone, are addressed in this chapter. Based on these studies, a new concept of "*in vivo* tissue fabrication" is proposed and its clinical perspective in the field of reconstructive surgery is also discussed.

2. Stem cells and skin regeneration

The repair of skin defects resulting from wound, burn or tumor surgery has remained a challenge to clinical surgeons. Autologous skin graft has been the "golden standard" for the replacement of lost skin. However, the source of the skin becomes a problem, especially for patients with large-area burn injury. Moreover, problems, like the morbidity at the donor site, scaring, and the graft failure, also put the doctors in dilemma. Looking for skin substitutes has been a focus in plastic surgery.

Skin is the largest organ of the integumentary system in the body, which plays a key role in protecting the body against pathogens and excessive water loss. Its other functions involves insulation, temperature regulation, and sensation. Normal skin is composed of two primary layers: the epidermis, which provides waterproofing and serves as a barrier to infection, and dermis, which connects with subcutaneous tissue and support the structure of epidermis. Another function of dermis is related with various glands and follicles located in it. Deep damage at dermis level, can not only cause the exposure of deep tissue, but also result in the function damage of the skin.

Skin tissue engineering begins with epidermal cell culture, however, such technique is limited by a fragile texture of the skin, which can be easily torn away from dermis. Moreover, without hair follicles and glands, such cultured skin doesn't have other functions as normal skin either. [1-3] Great development has been achieved in skin engineering with the finding of various stem cells, especially adult stem cells. Mesenchymal stem cells (MSCs), first isolated by Friedenstein et al. in 1966, are multipotent stem cells, which are able to differentiate into adipocytes, osteoblasts, and chondrocytes. [4] They are good source of cell transplantation because of their multi-directional differentiation, easy collection, and weak immunogenicity. It was later found that such heterogeneous group of multipotent progenitor cells can be harvested from several tissues, including bone marrow (BM), adipose tissue, skeletal muscle, fat, (umbilical cord) blood, amniotic fluid, and different fetal tissues. [5] MSCs therapy has provided alternative solutions for the repair and regeneration of various tissues and organs. Many studies have shown that BM-MSCs can promote wound healing by transdifferentiating into skin components. [6, 7] An important role of BM-MSCs has been found in recent study by Yang et al. that BM-MSCs can strengthen cell proliferation, collagen synthesis, vascularization, and growth factor release during skin regeneration. [8] Besides, some recent researches have shown that somatic cells can also be reprogrammed to an embryonic like state. Induced Pluripotent Stem Cells (IPSCs) are one of the examples. By being exposed to a defined set of transcription factors—Oct4, Sox2, Klf4, and c-Myc—and embryonic stem cell culture conditions, a differentiated cell type (e.g., fibroblast) can be reprogrammed to a pluripotent state and are capable of directed differentiation into various tissue types. One of the most exciting findings about these cells is that they can differentiate into a multi-potent keratinocyte lineage capable of forming a fully differentiated epidermis, hair follicles, and sebaceous glands in a reconstituted *in vivo* environment. [9]

Now the cell-based therapy has been further expanded with the use of various synthetic or natural engineered extracellular matrices. It has been reported that such matrices can improve cell survival and functions compared with the injection of isolated cells into the defect sites, by providing cells with suitable microenvironments. Lee et al. [10] dissociated epidermal and dermal cells in high-density suspension and let these cells reconstitute *in vitro* to generate its own matrix. After transplanted with a wound matrix, there cells went through a process similar as embryonic skin development and formed skin with full function. Despite of these encouraging results from the lab, many issues still remain to be settled, like the source of cells especially for those without enough skin on the body, the immune reaction if allogeneic cell source is used, the long *in vitro* expansion time to acquire enough cells, and the directional induced differentiation of stem cell to form a functional skin *in vivo*.

3. Stem cells and bone regeneration

The development of bone tissue engineering has brought great progress in the reconstruction of bone defects. Successful clinical application of tissue engineered bones have been found in various reports from craniofacial reconstruction in areas such as calvarial, orbital, and palatal bone defects to repair of long bone defects in the femur and articular osteochondral defects. [11]

During the early phase of bone tissue engineering, differentiated somatic cells, like osteoblasts from periosteum, have been seeded on a degradable scaffold to generate bone tissue. [12, 13] Such technique was later found to be limited in the source of cells and the morbidity at the donor site. According to the published literature, bone marrow derived mononuclear cells (BM-MNCs), BM-MSCs, adipose derived mesenchymal cells (ADSCs), stem cells from skeletal muscle and the stromal vascular fraction (SVF) have all been proved to have bone regeneration promoting effects and have been used for bone tissue engineering *in vit*ro or *in vivo*. [14-16] However, there is no consensus which type of cells is associated with better bone regeneration potential. Some studies have suggested that the osteogenic potential is similar between BM-MSCs and ADSCs, however, ADSCs might be a better alternative due to the lack of morbidity at the donor site. [17] Other studies also claimed that the avoidance of *in vitro* expansion might make SVF more suitable for clinical application. [15, 17]

Besides, various scaffolds, both biological and synthetic, have also been studied in this field. Bruder et al. used porous ceramic cylinders consisting of hydroxyapatite (65 per cent) and beta-tricalcium phosphate ceramic (35 per cent) with BM-MSCs for bone regeneration. [18] Arca et al. used acellular crosslinked porcine-derived cancellous bone graft with BM-MSCs for *in vitro* bone tissue engineering and an osteoinductive capacity was found in such material. [19] The choosing of scaffold material is largely determined by the bone defect itself. Fast resorbing materials, like tricalcium phosphates (TCP) can be used in a wound without special requirements of mechanical support, and slower degradation can be achieved by using materials like hydroxyapatite (HA) or through a combination of different materials, such as TCP and HA, or polyglycolic acid (PGA) and polylactic acid (PLA). [20]

Another progress in bone tissue engineering is using stem cells as gene therapy vector. Hao et al. found that osteogenic potency of ADSCs was enhanced by transfection with bone morphogenetic protein 2 (Ad-hBMP2). [16] In another study, ADSCs encoding VEGF was found to have a greater osteogenic capacity both *in vitro* and *in vivo*. [21] Moreover, enhanced vascularization was also observed by such genetically modified stem cells. Such combination of stem cells, scaffold, and gene therapy, not only extend the bone regeneration capacity of stem cells, but also help to improve the microenvironment for wound healing. [16, 20] Clinical success was also achieved by using cell-based tissue-engineering approach to treat patients with large bone defects. [22] Despite of great progress of bone tissue engineering has been made both from research and from clinical practice, further studies are still need to improve the isolation of cells, the construct of the scaffold, and the whole cell processing process to make it more suitable for clinical application.

4. Cartilage tissue engineering

Cartilage tissue engineering typically involves the combination of a biodegradable scaffold material with a certain type of cells to differentiate into chondrocytes. Previously, autologous chondrocytes were applied to generate cartilage *in vitro* as substitute of the

injured cartilage tissue. Such technique constituted the early cartilage tissue engineering, however, it is also limited by the source of cells as well as the morbidity left at the donor site. [23, 24] The progress of regenerative medicine has provided more alternatives for cartilage tissue engineering. Mesenchymal stem cells isolated from many tissues, including bone marrow, adipose tissue, synovium, and umbilical cord, have all been found to have a chondrogenic potential and can be applied for cartilage tissue engineering. According to a recent study, the chondrogenic potential is similar between BM-MSCs and ADSCs. [25] Besides, adipose stromal vascular fraction has also been proven to be a good alternative for cartilage tissue engineering. Without *in vitro* expansion, such cells are more practical for clinical application. [26] A variety of materials have also been proposed as scaffolds, which constitute another important factor of tissue engineering of cartilage. These scaffolds not only act as protection during cell delivery, but also provide structural support for the growth of cells. Now many scaffolds are also modified to recreating an extracellular environment that is similar to that *in vivo*. [27] With the limited source of natural scaffold, synthetic materials have gained tremendous development in the recent years. Instead of using single-element material, such as collagen, silk or hydrogel scaffold in the past, now more and more studies tend to use combined materials to adjust an optimal mechanical strength or degradation for better *in vivo* tissue formation, like silk-fibrin/hyaluronic acid composite gels or silk fibroin-chitosan combination. Such combinations have also been used to create a 3-D structure with spatially-varying mechanical properties to mimic the native extra cellular matrix (ECM) composition. [27-30]

Great progress has been achieved in cartilage tissue engineering during the past decades, however, some issues still remain in this area, for example the directed differentiation of stem cells, the simulation of actual physiological condition into the body, the integration of tissue engineered cartilage to the body, and so on. Growth factors have been found to be promising in the directed differentiation of stem cells. A combination of FGF-2 or FGF-6 with TGFβ2 has been proven by Bosetti et al. to be effective to induce the chondrogenic differentiation of MSCs. Similarly, TGF-beta3, BMP-6, and IGF-1 have all been found to have such effects. [31, 32] Studies have also been performed to address the issue of adjusting tissue engineered cartilage to the actual condition *in vivo*. Ronzière et al. found that reduced oxygen was associated with higher chondrogenic protential for both cultured BM-MSCs and ADSCs. [33] Besides, various bioreactors have also been introduced to increase the mechanical property of the tissue engineered cartilage. Tarng et al. found in their study that the composition of the engineered cartilage, including their ECM composition, cell distribution, zonal organization and mechanical properties, resembles native cartilage if shear stress and hydrodynamic pressure were provided simultaneously. [34]

Engineered cartilage has also become an alternative for auricular reconstruction in plastic and reconstructive surgery. Ruszymah et al. has constructed a human external ear with human cartilage cells and skin cells seeded on a high density polyethylene. [35] Positive clinical results have also been achieved by such technique. Neumeister et al. combined the techniques of vascular prefabrication, tissue culturing, and capsule formation to fabricate ear construct that is reliably transferable on its blood supply. [36] Despite of the encouraging progress, many improvements are still needed for its clinical application, such as to shorten the *in vitro* expansion time, to strengthen the mechanical property of the neocartilage, and to simplify the whole process.

5. Stem cells and vascularization

Flap surgery is often used in reconstructive surgery to repair defects resulting from trauma, congenital defects or cancer excision. Partial or complete flap necrosis is a common postoperative complication, which is mainly due to the lack of adequate nutrient blood flow resulting from vascular compromise. Tissue damage happens during sustained ischemia period and also happens during reperfusion period often initiated by a salvage surgery. [37]

Studies of vascularization process after flap surgery showed that the formation of new blood supply is achieved by two mechanisms: namely, angiogenesis and vasculogenesis. Angiogenesis refers to the sprouting of microvessels through a preexisting capillary network, whereas vasculogenesis refers to vascular formation from endothelial progenitor cells that differentiate or endothelia cells that proliferate *in situ*. With both mechanisms associated with the vascularization of flap postoperatively, a therapy focused on both mechanisms is supposed to be the most effective. [38, 39]

Cell-based therapy has become a new focus in this area. Previously, Park et al. injected endothelial progenitor cells (EPCs) into the systemic circulation of nude mice with cranially based random-pattern skin flap. [40] Three days after the treatment, EPCs began to appear around ischemia site and the vascular density increased significantly after EPCs administration. Later, better vascularization promoting effect was also verified by Yi et al. with EPCs encoding VEGF as gene therapy. [41] They found these gene-engineered EPCs not only showed greater ability of adhering and incorporating into newly formed vessels, but also enhanced native angiogenesis. According to these studies, EPCs not only showed great potential of incorporating into newly formed vessels, but also enhanced native angiogenesis.

Mesenchymal stem cells like BM-MSCs and ADSCs have also been proven to contribute to vascularization of ischemic tissue. [42, 43] On a random skin flap model, Lu et al. found that the transplantation of ADSCs can significantly increase the flap viability by differentiating into endothelial cells. [44] Other studies also show that ADSCs can promote endothelial cell proliferation and blood vessel formation through paracrine secretion of growth factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-b1, TGF-b2, hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF)-AA and et al. [45] Such effects have also been found in BM-MSCs. The regenerative stem cells not only act as a cell source for angiogenesis, but also secrete multiple growth factors to support angiogenesis. Besides, they can also be used as a vector for gene therapy without the problem of immune reaction or other problems that can be caused by a viral vector. [45, 46]

However, in most clinical settings, the occurrence of ischemia is unpredictable with rapid aggravation. There is no time for *in vitro* expansion the aforementioned stem cells. In the recent studies, both BM-MNCs and SVF, have been found to promote the survival of ischemic flaps. [47] With great progress in stem cell therapy, more optimal choices will appear for the treatment of ischemia flaps. But still what is known from these cells is not enough, lots of work have to be done to explore the mechanism of cell therapy, and to improve the survival of transplanted cells as well as their therapeutic effects.

6. Stem cells and breast tissue engineering

The removal of a breast has implications for the psychologic, social, and sexual well-being of the patient, establishing the essential need for breast reconstruction after mastectomy. Now breast reconstruction has been involved as an important part in the management of breast cancer. However, most of breast reconstruction has been achieved by autologous tissue transplantation, such as transverse rectus abdominis myocutaneous and deep inferior epigastric perforator flap. Although such autologous tissue reconstruction could bring great improvement in both appearance and texture to the defects, they are also associated with certain side effects, like great morbidity at the donor site, longer operation process, and the risk of flap failure. Looking for a safe and effective technique with less trauma to the body has been a key issue in breast reconstruction. [48]

Fat tissue has been considered as a good source of tissue for breast reconstruction and lipofilling has therefore been used frequently for the reconstruction of breast after mastectomy. However, large sum of lipofilling is associated with problems, like necrosis, cysts formation, and microcalcification formation. Some scientists have tried to solve this problem through tissue engineering. [49] Coleman et al have tried to enhance the nutrient supply as well as the survival of the fat tissue by microinjection. [50] Patrick et al., however, combined preadipocytes with porous scaffold of poly (L-lactic-co-glycolic) acid (PLGA) for fat transplantation. During the initial phase of the study, satisfactory results were observed by such method, however, after long-term observation fat tissue was found absorbed with the degradation of PLGA. [51] Based on these studies, Lin et al have further tried to combine ADSCs with a composite scaffold, made by a mix of gelatin sponges, polyglycolic acid, and polypropylene. Scaffolds were found to be filled with newly formed adipose tissue and had retained their predefined shape and dimensions after 6 months' *in vivo* transplantation. [52]

Despite of great success achieved in breast tissue engineering as proven in many publications, great concern has been arisen about the oncological safety about these techniques. More and more studies have shown ADSCs may either present as a source of tumor or provide an environment for the growth of the tumor, lipofilling combined with ADSCs and ADSCs based breast tissue engineering has been greatly impeded. [53-55] Another type of cells in the adipose tissue, SVF, may present as an alternative, however, studies are still needed to verify its safety. [56] Since still there has not been enough evidence showing that these techniques can indeed cause tumor clinically and great progress is still achieving in the understanding of cancer and stem cells, breast tissue engineering may still regain its prospect in the future. [57]

7. *In vivo* tissue prefabrication

With various flap surgeries in reconstructive surgery, soft tissue defects can now be repaired with better appearance and function, which cannot be achieved by skin graft. However, flap surgery is still challenged when there is composite tissue defect, including cartilage or bone. Autologous composite tissue transplantation has been used for such cases, but the great morbidity at the donor site often makes the doctor retreat from it. Allotransplantation of composite tissue has also been considered as a possible solution.

However, it is limited by immunological rejection, lack of proper donors, and some kind of psychological resistance.

Base on the traditional prefabricated flap technique in plastic surgery and tissue engineering, a new concept of "*in vivo* tissue prefabrication" has been proposed here. Prefabricated flap technique (or preliminited flap technique in some literature), first introduced in 1980s, refers to implanting the vessels and vessel carrier within multiple autologous tissues (bones or cartilage) and/or artificial material in the donor site that does not possess an axial blood supply. [58, 59] It potentially allows any defined tissue volume or components to be transferred to any specified recipient site, providing ideal solution to the repair of complex tissue defects. Using such technique, Kobayashi et al. has achieved successful total lower eyelid reconstruction on patients. [60] Besides, more complicated structures, like nose and ear, have also been successfully prefabricated. [61, 62]

Now with the progress of tissue engineering, many tissues, such as cartilage and bone, can be created by *in vivo* tissue engineering. Such tissue engineered cartilage or bone can be fabricated with skin, subcutaneous tissue, and blood vessel to be a composite tissue for defects repair. Okuda et al. has created tissue engineered bone by culturing adipose-derived stem cells with porous beta-tricalcium phosphate. After transplanted into superficial inferior epigastric artery flap, angiogenesis was successfully induced into the tissue engineered bone tissue and a compsite tissue flap including bone and muscle was also successfully prefabricated. [63] Similarly, Feucht et al. induced tissue engineered cartilage *in vitro* with chondrocytes from auricular biopsies. The cartilage-engineered constructs was then implanted beneath a random-pattern skin flap for prefabrication. 6 weeks later, the flap was elevated and transferred as a free composite flap. [64] Neovascularization was achieved in the tissue engineered cartilage and its growth was also maintained. The aforementioned studies have tried an *in vitro* way to generate tissue for later prefabrication, however, *in vivo* tissue engineering actually provides a better solution to the problem. By introducing cell embedded scaffold directly into the body, the process of tissue engineering and flap prefabrication can be combined, which not only reduce the time for both procedures, but also leads to more effective tissue engineering. For example, the *in vivo* environment can provide optimal conditions to facilitate functional tissue engineering. Moreover, with better vascularization *in vivo*, lager size tissue engineering can be achieved. [65]

8. Conclusions

In vivo tissue prefabrication technique, combining traditional prefabricated flap technique and tissue engineering, not only brings vascular supply to the engineered tissue, but also greatly reduce the morbidity at the donor site during traditional flap prefabrication. With the development of tissue engineering, many tissues can be generated *in vitro* or *in vivo*. Combined with prefabrication with various tissue types or with better blood supply technique, such cultured tissues can be prefabricated for repair and reconstruction. In the future, more complicated parts on the body, like ear, nose or thumb, may also be prefabricated. Moreover, according to the recent studies, neovascularization, the key to a successful prefabrication, can be enhanced and greatly speeded with stem cells transplantation, which means a perfect substitute of the lost body part can be generated in shorter time in the future.

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Selected Topics in Plastic Reconstructive Surgery

Edited by Dr Stefan Danilla

ISBN 978-953-307-836-6
Hard cover, 242 pages
Publisher InTech
Published online 20, January, 2012
Published in print edition January, 2012

Plastic Surgery is a fast evolving surgical specialty. Although best known for cosmetic procedures, plastic surgery also involves reconstructive and aesthetic procedures, which very often overlap, aiming to restore functionality and normal appearance of organs damaged due to trauma, neoplasm, ageing tissue or iatrogenesis. First reconstructive procedures were described more than 3000 years ago by Indian surgeons that reconstructed nasal deformities caused by nose amputation as a form of punishment. Nowadays, many ancient procedures are still used like the Indian forehead flap for nasal reconstruction, but as with all fields of medicine, the advances in technology and research have dramatically affected reconstructive surgery.

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