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Review Article

The Scope of Stem Cell Transplantation in Tissue and Organ Regeneration: Myth or Reality?

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Abstract

Transplantation of stem cells to regenerate and repair damaged organs offers promising scope for treating various debilitating diseases and is a feasible alternative to organ transplantation, owing to the ability of stem cells to repopulate the engrafted site by differentiation or trans-differentiation. However, before stem cell-based therapies could be transferred to clinic many challenges such as controlling the self-renewal, differentiation efficiency, and integration of engrafted stem cells or differentiated cells to the host milieu need to be optimized. In this review, we summarize strategies that have been used in stem cell-based regenerative medicine and in particular, feasibility of stem cell therapies in restoring damaged tissue and organs.

Keywords: Stem cell; Regeneration; Therapy; Scaffold; Biomaterial; Differentiation

Abbreviations

ES: Embryonic Stem cells; EG: Embryonic Germ Cells; iPSCs: induced Pluripotent Stem Cells; SCT: Stem Cell Therapy; MSC: Mesenchymal Stem Cells; MAPC: Multipotent Adult Progenitor Cells; MIAMI: Marrow-Isolated Adult Multilineage Inducible cells; ADSC: Adipose Derived Mesenchymal Stem Cells; CSCs: Cardiac Resident Stem cells; SPOC: Skeletal Progenitor cells for Cardiomyocytes; ECM: Extracellular Matrix; HCN2: Hyperpolarization-activated Cyclic Nucleotide-gated ion channel 2; SP: Side Population cells; GH: Growth Hormone; FSH: Follicle Stimulating Hormone; LH: Leutinizing Hormone; ACTH: Adrenocorticotropic Hormone; TSH: Thyroid Stimulating Hormone; ABCG2: ATP-Binding Cassette Sub-family G member 2; SJS: Stevens-Johnson Syndrome; LSCD: Limbal Stem Cell Deficiency; OA: Osteoarthritis; ACT: Autologous Chondrocyte Transplantation

Introduction

Tissue regeneration from stem cells is an old concept way back to 1961 by McCulloch and Till when they demonstrated different lineage of blood cells from a common origin of a stem cell [1]. Regenerative capabilities of vertebrates at certain tissue regions have limitations, either they do not regenerate after adult form or regeneration rate is very poor [2]. The more maturation of a cell type happens, the lesser regenerative capability ensues. The best example is myocardial cell repair after myocardial injury from infarction. Whatever extent of damage is produced, 5% recovery of the tissue loss can be expected [3,4]. Greek mythology based liver recovery of Prometheus though stands a scientific basis of replenishment of certain tissue in the body after injury, it is evident that the invertebrates and non-mammalian vertebrates develop this kind of replenishment very fast at every sectors of the body, if limbs are cut they grow their limb. For example, Planarians and non-mammalian vertebrates such as salamanders and teleost fish exhibit an extraordinary ability to regenerate lost body parts much more effectively than mammals [5].

Clinical research has progressed to a great extent towards preventing, diagnosing and managing debilitating diseases. Culture of human stem cells, including embryonic stem (ES) cells, embryonic germ (EG) cells, induced pluripotent stem cells (iPSCs) and adult stem cells provide unique opportunities for studying and understanding molecular basis and pathophysiology of heart diseases, liver failures, diabetes, cancer and diseases of the nervous system. It was widely believed that tissue-specific stem cells are the prime candidates that differentiate into mature cells of the respective tissue. Present status of great advancement in stem cell technology, the information we have is that ES cells have greater capability of producing required tissue provided the same cue is given to them. Derivation of ES cells from early human embryos, and embryonic germ cells and fetal stem cells from aborted fetuses, raise ethical, legal, religious, issues [6]. The recent breakthrough in the field of iPSCs have opened up a new era in the field of stem cell based tissue regeneration, wherein patient-specific stem cells can be generated from mature cells that can regenerate the tissue or organ of interest. Immune rejection posing a major threat to the success of stem cell transplantation, particularly for the embryonic stem cells-derived phenotypes in allogenic recipients due to histoincompatibility [7,8], recent attempts to generate immune-protected ESC-derived allografts [9] garner some hopes for future. Due to the unique immunomodulatory property of suppressing T cell alloreactivity [10], autologous adult stem cell transplantation [11] as well as allogenic mesenchymal stem cell therapy [12] has been successful in clinical trials. Therapeutic potential of iPSCs was questionable due to previous findings reporting immunogenicity of iPSCs-derived teratoma in syngeneic hosts [13]. However, recent reports suggest that syngeneic "self"-iPSCs and their derivatives are immunotolerant in the host [14,15] supporting their safer clinical use in cellular therapy. Despite significant progress in the stem cell-based research, the potential uses of stem cells for regenerating human tissue and perhaps organs are the subjects of ongoing public debate.

Various clinical studies have confirmed that adult tissue-specific stem cells exhibits plasticity and differentiate or trans-differentiate to

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cells of various lineages. As a result, we could envisage experiments converting a single undifferentiated cell or a fertilized egg, into the different cells comprising the organs and tissue of the human body. To think rationally, human being, an advance mammalian species does not have simple mechanism of organ development. Many organs such as heart, liver, kidneys etc. have complex developmental biology. However, it is plausible that organs or tissue with singular or similar cell types can be addressed by stem cells during their loss. In this review, we discuss the feasible strategies using various categories of stem cells combined with biomaterials scaffolds for regeneration of various tissue and organs.

Stem cell based regeneration of various tissue and organs

The stem cells with varying origin such embryonic and adult tissue as well as iPSCs with varying differentiation efficiency have been induced towards specific lineage with the hope of regenerating tissue and organs of interest, by using scaffolds of natural and synthetic origin [16,17]. Major applications of stem cells in regeneration of various functionally important tissues have been depicted in Figure 1 and illustrated in details as follows.

Cardiac Regeneration

The human heart is considered as post-mitotic organ and has limited capacity for regeneration [18]. Stem cell therapy (SCT) to injured heart can improve the tissue regeneration and contractile ability of infarcted heart [19]. For treatment of cardiomyoplasty, hematopoietic stem cells expressing CD34 and/or CD133 have shown significant regenerative capacity in the infarcted dead myocardium of rats [20]. However, the multipotency of adult human stem cells similar to that of murine counterparts for cardiac regeneration still undefined *in vivo*. Moreover, therapeutic applications of aforementioned cells for cardiomyoplasty have been inconsistent, since it is yet to define the participation of single bone marrow stem cells in cardiac regeneration process [21,22]. C- Kit positive cells from bone marrow efficiently differentiate into myocytes and can be excellent source for transplantations [23]. Endothelial progenitor cells, which are functionally and phenotypically different from mature endothelial cells derived from cord blood, peripheral blood or bone marrow can also be efficient cells for remodeling the heart [24]. In an initial clinical trial study involving autologous stem cell transplantation in treating patients with severe myocardial dysfunction has shown promising results [25]. This study involved injection of autologous peripheral blood-derived endothelial precursor cells in 11 patients and autologous bone marrow mononuclear cells in 29 patients. A marginal improvement in myocardial function was noted at 3 months (mean increase in ejection fraction), although it plateaued at 6 months. With this result, there is growing optimism that stem cell therapy may delay heart transplantation. Mesenchymal stem cells (MSC), multipotent adult progenitors (MAPC), marrow-isolated adult multilineage inducible (MIAMI) cells derived from bone marrow, adipose derived mesenchymal stem cells (ADSC) are also considered to be excellent therapeutic cells for cardiomyoplasty [26-31]. Some of the cardiac resident stem cells (CSCs), which are positive for c-kit, Sca-1, Isl1 and which have ability to form cardiosphere appear to be the ideal cell sources for myocardium regeneration in

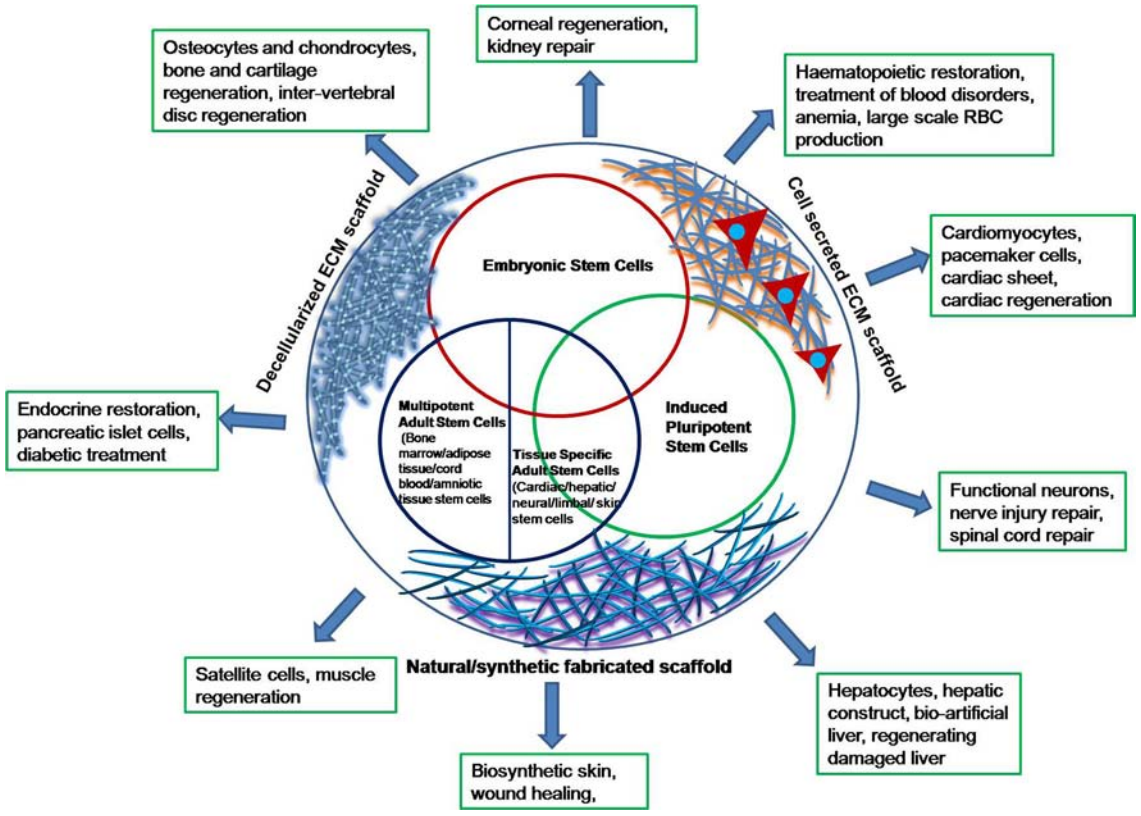

Figure 1: A schematic representing interaction between stem cells and biomaterials scaffold for functional regeneration of various tissue and organs. The overlapping zone between three central circles represents similar potency and gene expression profiles of three kinds of stem cells.

both humans and murines [20-22]. Researchers had identified that skeletal progenitor cells for cardiomyocytes (SPOC) and skeletal myoblast cells derived from muscle can also regenerate the heart [31,32].

It is important to use a mechanism that would allow cell homing to the site of injured myocardium. The homing can happen in a scaffold which is biocompatible and congenial for cell proliferation and function. It could be thermo-responsive gels or synthetic/natural biodegradable polymer or peptide in nanoscale or biopolymer as such. Recently, advent of myocardial patch consisting of a strong scaffold with stem cell impregnation has entered the arena of myocardial repair [33]. The possibility of dead myocardium harvested as homograft within 24 hours of death can be transformed into biological myocardial assist device as proved by Guhathakurta et al. [34]. This could be achieved with adult progenitor stem cells injected into the scaffold and subjecting the scaffold to dynamic forces equivalent to electrical and mechanical forces experienced by normal myocardium in physiological conditions. The scaffold receives the cells and then cell-cell talk and cell-ECM (extracellular matrix) talk take the construction of tissue further. This procedure holds good for every tissue but the polymer or gel may be different. Cardiovascular regeneration involves heart valve regeneration by stem cells in an acellular scaffold [35,36] as well as vascular tissue formation by tubular scaffold [natural or synthetic] seeded with stem cells. Endothelial progenitor cell seeding on a tubular scaffold is another way of developing blood vessels [37,38]. Moreover, cardiac tissue-conditioned prepared from ischemic tissue is reported to induce cardiac differentiation of human mesenchymal stem cells, expressing markers of precursor cardiomyocytes [39]. Biological pacemaker generation from stem cells by transfecting with HCN2 gene is in progress and successful experiments were made in canine models [40]. In summary, regenerating the entire heart may not be a possibility but part by part repair may be a feasible option in future.

Hepatic Regeneration

The hepatocytes, in particular oval cells, have the potential to undergo several rounds of division to replace the liver mass after injury or cirrhosis. For treating end-stage liver failures, liver transplantation is the most effective treatment, but it is limited by donor availability, rejection risk, and high cost involved. Direct hepatocyte transplantation has been used as a therapeutic alternative to whole liver transplantation [41,42], but their long term survival during transplantation still raises some concern. Stem cell therapy is an attractive modality in this regard, as it has the potential to regenerate damaged liver in diseases like hepatitis, non-alcoholic fatty liver disease, cirrhosis, liver cancer, Wilson's disease, Primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune disease of small bile ducts, Budd-Chiari syndrome, Gilbert's syndrome, glycogen storage disease [43,44]. The hepatic stem cells, present both within and outside the liver can differentiate into mature hepatocytes after their transplantation into the liver [45]. Reports suggest that bone marrow derived -mesenchymal stem cells could effectively rescue experimental liver failure and contribute to liver regeneration and hence it can offer a potentially alternative therapy to organ transplantation for treatment of liver diseases [46]. Recently, human bone marrow mesenchymal stem cells have been trans-differentiated towards functional hepatocytes using sera from cardiac-failure associated ischemic/congestive liver, which is clinically relevant [47]. Also, CD34 positive cord blood stem cells have been reported to treat liver diseases, which can be another effective option for liver failure treatment [48].

Currently, there is usage of various extracellular matrix scaffolds including polymeric nanofibrous scaffolds that supports hepatic trans-differentiation of mesenchymal stem cells [49] with a combinatorial strategy that employs both physical and humoral cues in guiding stem cells towards functional hepatospheres. Moreover, low frequency magnetic field exposure ameliorates enhanced differentiation of human mesenchymal stem cells on a biomagnetic scaffold fabricated from blood clot-polymer mixture [50]. Such a scaffold containing stem cell-derived hepatocyte can be used as a graft in the injured liver for enhanced hepatic regeneration *in vivo*. However, a battery of tests such as biocompatibility, cytotoxicity, biodegradability, hepatotoxicity etc. needs to be performed before proceeding to such clinical initiatives. Nevertheless, such a novel hepatic tissue engineering approach has tremendous scope for treating various end-stage liver diseases.

Regeneration of Neural Tissue

Stem cells located in adult central nervous system, have a poor capacity to generate new neurons after injury or degeneration. Although the stem cell therapy offers tremendous scope in treating nervous system disorders, issues relating to proliferation and differentiation of stem cells into functional tissue of interest needs to be evaluated [51]. It is reported that spinal cord repair using stem cells has adverse side effects in a rat model [52]. Therefore, an optimized and safe protocol for guided differentiation of transplanted stem cells needs to be assessed before proceeding for stem cell-based therapy in neural disease treatment. There have been encouraging reports of deficit reduction and axonal regrowth by stem cells and scaffolds implantation [53]. It was shown that the extent of functional recovery and neural networking was elevated by transplantation of stem cells on polymeric scaffolds than the transplantation of stem cell alone in a spinal cord injury model [54]. In a proof- of -concept style, various synthetic extracellular mimics have been tried in neural tissue engineering. In one report, glial scar formation was inhibited by using self-assembling nanopeptides, simultaneously promoting axonal elongation after spinal cord injury [55]. In another study, RADA-16 nanopeptides have also promoted reconstruction of acutely injured brain [56]. The use of exclusively designed bioactive matrix made from nanopeptides [e.g. IKVAV, RADA-16] could provide important clues to develop a clinically relevant technique that might advance recovery from nerve injury. However, various parameters such as optimal fiber diameter, inter-fiber distance as well as suitable biomechanical properties of nanoscale scaffolds need to be fine tuned, which are of paramount importance in neural tissue engineering. A recent breakthrough in the field of neural tissue engineering reports construction of a bioengineered functional 3D brain-like cortical tissue by using silk-based scaffold, ECM derivatives and primary cortical neurons, offering great hopes for future clinical applications [57].

Skin Regeneration

Although, autologous grafts are used successfully to treat skin

disorders, the major disadvantage of grafts is the need for a large amount of donor skin. Synthetic and biosynthetic matrices containing adult allogenic skin cells and bovine collagen are alternatively proposed without a guarantee of the necessary safety, especially in terms of graft rejection [58]. Cell therapy and cell-culture techniques have been used to reconstruct the damaged epidermis. Adult human keratinocytes and epidermal stem cells can be expanded and may be subsequently transplanted as a biological dressing in burn injuries, chronic wounds, and various skin diseases [59]. Successful transplantations of autologous cultured melanocytes have been done on patients with severe skin disorders. Long-term efficacy of transplantations has also been well established. Several studies have documented the efficacy of different cellular methods such as pigment production, long-term results, and their relative efficacy in difficult areas [60]. Many studies that used autologous cultured melanocytes-epidermal grafts have also documented impressive results. These results have led to the commercial availability of cell therapy based products. Isolation and expansion of hair follicles derived- melanocyte stem cells offers promising scope ahead in cosmetic industries. For long term engraftment of the regenerated skin, parameters like source, quality and adequate culture conditions of epidermal stem cells are of prime focus. In addition, it is likely that tissue-engineered skin construct will comprise the priming epidermal stem cells to kick-start generation of epidermal component and further supplementation of melanocytic stem cells to it to make it more functional [61]. For the dermal construct, it is likely that endothelial, mesenchymal, neural and/or other primitive stem cells may help with generation of dermal components including a new vasculature. Such a construct should mimic the natural skin functionality in terms of barrier formation, pigmentary defense against UV irradiation, thermoregulation, as well as mechanical and aesthetic functions.

Muscle Regeneration

Skeletal muscles possess a complex array of multi-nucleated muscle fibers, satellite cells and precursors capable of generating new muscle fibers. Under normal physiological conditions, skeletal muscle takes up self- repair mechanism by replenishing itself with new muscle fibers in place of damaged ones. Although, satellite cells are potential candidates for muscular regeneration, they are in low numbers, difficult to maintain *in vitro* and undergo rapid senescence [62]. Hence, the other cellular counterparts such as muscle resident side population cells (SP cells) [63,64], mesenchymal stem cells derived from various tissue [65-68], haematopoietic stem cells [69,70], stromal cells derived from synovial membrane [71], CD34 positive endothelial cells and mesangioblast derived stem cells [72] are considered potential candidates to repair and regenerate muscle by various animal experimental studies.

Endocrine Restoration

Endocrine glands are a group of specialized cells which possesses the ability to secrete their products, called hormones, directly into the systemic circulation and exerting their effects on the efficient functioning of the body. The key endocrine glands of the body include the pancreas, pituitary glands, ovaries, testes, thyroid and parathyroid glands and adrenal glands. The secretions of these glands, viz. the hormones govern many vital functions of the human body as corroborated by the number of diseases manifested in the event of reduced and hyper function of these glands. Hormone replacement has been the therapeutic intervention of choice, but has its own caveats including increased risk for breast cancer, cardiovascular disease, cancer, in addition to decrease in responsiveness to the administered dose of hormones after a long term treatment. Optimization of the correct dose of the hormone to be administered is also a bottle neck in this treatment strategy. In the case of decreased endocrine function due to an autoimmune disorder as in the case of Addison's disease or hypothyroidism, hormone replacement therapy does not prove effective even at very high doses.

With the increasing usage of stem cells as a therapeutic intervention to treat various disorders, the role of the same in treating patients with decreased endocrine gland function is rapidly emerging as a successful trend. The modern lifestyle changes have brought forth a variety of reproductive system dysfunctions including early menopause, male and female infertility. Stem cell therapy has shown to increase the levels of estrogen, progesterone, follicle stimulating hormone, leutinizing hormone, prolactin, cortisol, thyroid hormones, thyroid stimulating hormones which has a direct/ indirect effect on the efficient functioning of the reproductive system [73]. There have been reports of adverse effects following SCT in the treatment of various hormonal deficiencies including cases of development of hyperthyroidism/ autoimmune hypothyroidism post-stem cell therapy [74,75] thereby cautioning practicing doctors to have a thorough case evaluation before deciding on the adoption of SCT to treat these disorders. Lifelong levo-thyroxin is required for patients with hypothyroidism. The other option is thyroid tissue autotransplantation. There are many studies to prove that adult stem cells reside in thyroid gland but these cells do not express terminal thyroid differentiation markers such as thyroglobulin and calcitonin. However, there is no evidence till date that these cells are capable of thyroglobulin synthesis [76]. Animal experimental studies with embryonic stem cells engrafted into adult rodent pituitary gland could survive for 4 weeks and express Pit-1, GH (growth hormone), FSH (follicle stimulating hormone), LH (leutinizing hormone), ACTH (adrenocorticotropic hormone), and TSH (thyroid stimulating hormone). However, more experimental confirmations need to be ascertained before initiating targeted cellular therapies [77]. The dysfunctional organ may be loaded with stem cells and may be used as receptor scaffold under immunosuppression in autoimmune diseases.

Diabetes mellitus is a metabolic disease caused by absent or insufficient insulin production from pancreatic beta cells. It is also associated with serious other complications, such as cardiovascular disorders, kidney disease, and blindness [78]. Cellular therapy with insulin producing cells from donor islets of Langerhans is an ideal treatment to this disease. Due to lack of donor organs and lifelong immune-suppression therapy other options such as differentiating stem cells to B cells are explored [79]. There are many types of cells reported for beta cell replacement such as adult stem cells isolated from pancreas [80] , liver [81,82], neural progenitors [83], bone marrow, Isl-1 induced expression of mesenchymal stem cells [84], side population cells present in Islet of Langerhans expressing ABCG2 [85] and *in vitro* modified human peripheral blood monocytes [86]. Transplantation of islet cells has been an alternative for long-term insulin administration and has met with

moderate success in spite of challenges including immune rejection etc. Multipotent stem cells, capable of differentiating into any lineage based on the microenvironment, have been used to replace the lost or diseased pancreatic beta cells. Both adult and embryonic stem cells when provided with the right environmental cues have proven to be potential sources of beta cells and have been characterized in detail. Phosphoinositide 3-kinase inhibitors when added to the culture media promoted differentiation of embryonic stem cells [ESC] into functional β- cells [87]. These cells produce insulin and secrete the same in response to glucose, with the typical intracellular calcium fluctuations seen in beta cells. Such ESC derived insulin-producing cells display the cell surface markers characteristic of beta cells and when implanted into mice, reversed diabetic conditions thereby providing a beacon of light in treatment strategies for diabetics. Current research focuses on reliable and efficient methods of differentiating these cells into specific lineages.

Eye Regeneration

Stem cell treatment is a successful option for patients with limbal stem cell deficiency (LSCD) which is resulting from severe ocular surface disease with chemical or thermal injury, Stevens-Johnson syndrome (SJS) and ocular cicatricial pemphigoid [88]. Although corneal transplant is the known conventional treatment, the availability of the graft is the major problem. Some researchers use ocular reconstruction with amniotic membrane and limbal stem cells are effective to some extent [89]. Limbal stem cells can be obtained as an autograft from the fellow eye in unilateral cases and as an allograft from related donor or cadaveric donors for the bilateral cases. Although there are many scaffolds and carriers such as autogenous conjunctiva, mucous membrane grafts, collagen lattices, synthetic implants the most widely accepted universal substratum for limbal stem cell niche is human amniotic membrane [90].

Bone and Cartilage Regeneration

Although the bone tissue contributes to its self turn-over, it does not possess enough capability to recuperate heavy bone loss due to physical trauma or in case of metabolic disorders such as osteoporosis. Stem cells from mesenchymal origin have been reported to contribute to osteogenesis [91] and trials are ongoing for treatment of osteoporosis [92]. Stem cell-based bone tissue engineering on various scaffolds has been proven successful with a possibility of clinical translation in future. In bone degenerative diseases such as osteoarthritis (OA), stem cells isolated from patients have reduced proliferative capacity and reduced ability to differentiate [93]. Various stem cell experiments using mesenchymal stem cells in caprine OA model had proven the reduction in OA progression in the cell-treated joints [94,95]. Shah and colleagues recently proved that growth factor delivery from a polyelectrolyte multilayer could promote bone tissue regeneration and repair in a critical-size rat calvaria model [96]. For cartilage regeneration, autologous chondrocyte transplantation (ACT) for knee injury patients has successful outcomes [97]. Also, various next generation biomaterials have been used as carriers for articular chondrocytes in cartilage tissue engineering, which offer great hopes for clinical applications [98].

Kidney Regeneration

Rare availability of kidney donors as well as the rejection risk related to kidney transplantation during renal failure has led the researchers as well as clinicians to explore feasible alternatives. Renal stem cells have been reported to be possible candidates for therapeutic application during acute and chronic renal failure [99,100]. The bone marrow stem cells have also been shown to participate in regeneration of the proximal tubule; however, the mechanisms remain controversial. Bone marrow MSCs have been differentiated *in vitro* into a renal epithelial lineage in a coculture model with injured renal cells, which raises hopes for treatment of renal failures [101].

Hematopoietic Restoration

Haematopoietic stem cells have been in the forefront of adult stem cells research in restoring various blood disorders such as leukemia and lymphomas, anemia, Thalassemia major etc. due to their high prevalence and easy accessibility. Autologous stem cell transplantation can be done in some diseases such as lymphoma [102], whereas for diseases like acute myeloid leukemia allogenic hematopoietic stem cells are preferred [103]. Although allogenic bone marrow stem cell therapy for blood disorders seems highly plausible and desirable, concerns relating to rejection and leukemic transformation of the transplanted cells need to be assessed.

Conclusion

The most exciting application of stem cells could be their potential use in replacement of poorly functioning tissue such as aged muscle or cornea; replacement of veins; coronary and peripheral stents; replacement of the bladder and fallopian tube; and restoration of cells to produce necessary enzymes, hormones and other bioactive secretory products. More importantly, certain chronic surgical conditions such as peri-anal fistula, which requires repeated surgeries due to nagging recurrence, can be addressed with adult progenitor/ adipose derived adult stem cell injection after primary surgery [104]. There are many types of stem cells suggested to be safe for cellular therapy based on murine and human experiments. However, substantial challenges such as heterogeneity, differential proliferative and differentiation capacities of stem cells have to be overcome. If appropriate chemical and physical cues, biomechanical parameters and preferably a biodegradable homing receptor/scaffold are provided, stem cells could be used to restore organs in near future. Experiments on aforementioned strategies could open up a common pathway to simplify the modus operandi towards stem cell use in injured body parts. A simpler method of differentiation and plasticity can be derived, which is very much lacking in our stem cell technology research day to day. Methods to isolate pure, native stem cells and for robust characterization of expanded stem cells have to be established. This would in turn contribute to the establishment of a reliable quality control system for clinical applications of stem cells.

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