



IJRASET

International Journal For Research in
Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 10 **Issue:** VII **Month of publication:** July 2022

DOI: <https://doi.org/10.22214/ijraset.2022.45546>

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The Comprehensive Review on the Approach of Kidney Regeneration; Using Stem Cells

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Abstract: Organ regeneration is an area of biomedical study that focuses on replacing an organ's cells to repair tissues and organs and partly or totally restore their original function. This article provides an overview of organ regeneration using stem cells and their potential use for treating kidney disorders. Compared to other organs, the kidney is a sensitive organ with a relatively low capability for regeneration. Renal disorder is becoming a public health concern. There are many progressive therapies to deal with such problems, but still mortality rates among subjects remained above average. Stem cell approach has been identified as a potentially effective approach in the search for novel therapies for promoting kidney regeneration. It is an excellent and promising alternative treatment to current therapies because this can provide a cure to kidney diseases and injuries without a transplant or dialysis. The stem cell therapy can be considered for the repair and kidney tissue regeneration. Different stem cell types and their mechanism have been discussing in this article. Also, the serious diseases caused by renal dysfunction are focused here such as AKI and CKD, the most common clinical issue in critically ill patients effecting around 50% and 18% of global population respectively.

Keywords: Kidney regeneration, stem-cells, tissue regeneration, AKI, CKD

I. INTRODUCTION

Incurable illnesses or physical wounds cause organ and tissue damage, which shortens a person's life; therefore, efficient therapies are needed for the treatment. The technique of Organ regeneration belongs to the process of generating specialized cells [1]. Such cells are referred to as stem cells because they maintain their proliferative ability throughout life. The special human cells known as stem cells can distinguish into a wide variety of cell types and have self-renewal capacity [2]. Injured parts of the body are the focus of stem cells, which gradually migrate and then attached to the host tissues and differentiate into new cells [3].

Based on their potential for differentiating, these cells may be categorized as pluripotent, totipotent, multipotent, unipotent, and oligopotent. TSCs can proliferate and give rise to all the cells in an organism. It has the greatest capacity for differentiation and enables cells to create both extra-embryonic and embryo structures [2]. One kind of totipotent cell is the zygote, which develops into three layers of germ tissue or a placenta following fertilization. All three germ layers can be formed by pluripotent stem cells, but extra-embryonic structures cannot. MSCs can divide repeatedly to replenish themselves and may differentiating number of specialized cell types. One form of multipotent stem cell that may be differentiating many blood cell types is the hematopoietic stem cell (HSCs) [2]. HSCs can only grow into a few numbers of cell types like myeloid or lymphoid stem cells, after differentiating [4]. Unipotent stem cells are incapable of differentiating numerous cell types and may only divide repeatedly into one kind of cell, such as dermatocytes. This article provides an overview of organ regeneration using stem cells and their potential utility for treating kidney disorders.

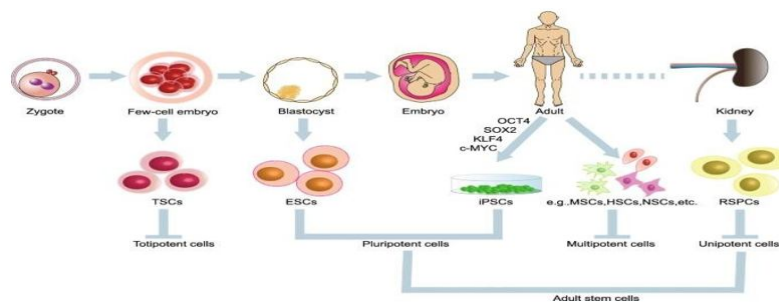


Fig. 1 Stem cell classification as per differentiation ability. TSCs (“Totipotent stem cells”), MSCs (“Multipotent stem cells”), PSCs (“Pluripotent stem cells”), iPSCs (“induced pluripotent stem cells”), ASCs (“adult stem cells”), ESCs (“embryonic stem cells”) (Liu et al. 2020).

Around 10% of the overall population of the world [1] is impaired by renal disease, which accounts for 5-13 million fatalities per year, mostly as a result of rising rates of diabetes, obesity, cardiovascular, and hypertension disease [5]. Because of its complex anatomical structure, it is more difficult to regenerate the human kidney than any other organ [6]. Both renal repair and nephron regrowth are components of kidney regeneration. Multidrug therapy, as a standard treatment for kidney illness, can't reverse the progression of ESRD in most people, and such persons need renal replacement treatment, such as dialysis, which is not considered as best therapy or kidney transplantation. To restore renal function, kidney transplantation may aid patients, however, the lack of donors and organ rejection restrict its usefulness [1]. CKD and AKI are two distinct diseases of kidney disease [5]. AKI is a disorder where kidneys are unable to remove waste from blood, and it often occurs in critically sick patients, where the incidence ranges from 15% to 50% [7]. Long-term kidney disease (CKD) is the underlying cause of renal dysfunction. Worldwide, the occurrence of CKD is increasing and impacts roughly 18% of people. The clinical research on cell-based therapy for renal illnesses is included in this review, together with a discussion of the difficulties and potential future directions for its use in treating kidney disease [8].

II. DIFFERENT STEM CELL TYPES AND THEIR ROLE IN KIDNEY REPAIR

A. Mesenchymal stem cells

These cells are fibroblast-like multipotent stem cells. They can multilineage differentiation and self-renewal. MSCs can be classified into several types, as these cells are isolated from different sites of the body such as tooth pulp, umbilical cord, periodontal tissue, gingiva, adipose tissue, amniotic fluid, skeleton muscles, etc. Cells derived from adipose tissue are widely used for research purposes, due to their abundance and easy extraction [9]. MSCs express CD105, CD73, and CD90 as surface markers and lack the hematopoietic expression markers such as CD45, CD34, CD794, CD14, CD116, and HCA-DR [10]. Moreover, MSCs consist of some immunoregulatory properties: T-cells expansion, shifting macrophages to anti-inflammatory and immune suppressive M2 phenotype, and inhibits Antigen-presenting cells [10]. They also suppress the functioning of B-cells, memory T-cells, and NK cells, therefore favorable to renal cells. Kidney repair via this therapy may not be eliminated by immune system [11]. Apart from immunoregulatory properties MSCs assist the tissue repair in damaged organs. Their protective effect on acute kidney injury has been demonstrated in various experimental observations [12]. Injection of MSCs-derived micro-vesicles after injury increases functional recovery and improves survival in lethal models of AKI. ATP (Adenosine triphosphate) supply is improved by micro-vesicles and transfer of mitochondria into the damaged cells [11, 13]. MSCs aid in cellular repair programs by releasing several growth factors like IGF ("Insulin-like growth factor"), "fibroblast growth factor", "hepatocytes growth factor", stromal cell-derived growth factor, and "vascular endothelial growth factor". Nitric oxide (NO), IL-10, IL-6, TGF- β , and other MSC-related mediators help to further promote a local anti-inflammatory state, which promotes the repair of injured tissues [13].

B. ESCs

These cells are obtained from the inner cell mass of blastocysts. These cells are termed PSCs as they may differentiate into each cell type of an organism and can give rise to the whole organism [14]. The majority of ES cells come from eggs that have undergone in vitro fertilization rather than in-vivo fertilized eggs. They may undergo lineage commitment into the three embryonic derivatives, the endoderm, ectoderm, and mesoderm, making them self-renewing and clonogenic [5]. Due to the complex anatomy and precise nature of renal structure, the kidney has become the most complex organ to reconstruct. Several protocols are considered to differentiate ESCs for generating complex structures similar to kidneys, termed organoids. These consist several multiple renal cell types and can organize themselves [14]. If eight different growth factors; are cultivated with human embryonic stem cells; TGF- β 1 ("transforming growth factor β 1"), activin-A, bFGF (basic fibroblast growth factor), HGF ("hepatocyte growth factor"), BMP-4 ("bone morphogenetic protein-4"), β -NGF (" β -nerve growth factor"), EGF ("epidermal growth factor"), and retinoic acid they will eventually develop into cells that produce renin and WT-1. Additionally, it is demonstrated that wnt4-transfected mouse embryonic stem cells may develop into tubular-like structures that express aquaporin-2 when HGF and Activin A are present [13]. Mouse ES cells show an increase in differentiation into renal progenitor cells intermediate mesoderm when cultured with CCG1423 and LY294002 combination and Janus linked tyrosine kinase inhibitor1 [14]. To test the potential of ES cells differentiating into renal cells, Steenhard et al. studied an ex-vivo culture method in which ES cells were microinjected into growing metanephrons. A structure resembling a tubule, as well as a tuft of kidney glomeruli, included the identified renal epithelial cells and a few ES cells [15]. Activin A, retinoic acid, and BMP-4-treated ES cells contributed to tubular epithelium nearly completely when they were injected into growing metanephrons [16].

Although, the therapeutic use of human ES cells causes two significant issues. One is the ethical issue of using donated eggs to create ES cells, and other is the immunological rejection because of histocompatibility antigenic discrepancies between ES cells and subjects [17]. ES cells are a significant supply of cells for studying cell development, however, they are not ideal for clinically applied regeneration treatment.

C. iPSCs

Cells derived from blood or skin can be induced to become PSCs by presenting core transcription factors that are Sox2, Oct3/4, and Nanog; such cells are termed as iPSCs [18]. These cells are an unlimited source of any type of human cells required for therapeutic purposes. iPSCs are another type of stem cell that is a potential source for treating kidney disorders [19]. Human kidney development and disease may now be studied in-vitro using new in-vitro platforms created from iPSC differentiation into Nephron progenitor cells and organoids. The organoids enable to review of the abnormalities by evaluating the cells at every differentiation phase [20]. Administration of human iPSCs that developed into metanephric mesenchyme and subsequently nephrogenic intermediate mesoderm might engraft and aid kidney recovery from cisplatin-induced AKI, according to Morigi's research. Transplantation of human iPSC-derived renal progenitor cells beneath the kidney capsule prevents the development of renal failure and fibrosis [19].

D. BMDCs and ADMSCs

As a result of the vast number of stem cells found in the bone, the bone provides significant support for HSCs ("hematopoietic stem cells"). Other organs have long been recognized to use stem cells from the bone marrow [21]. Numerous studies have shown that BMDCs can enter the kidneys and have a vital contribution to the activation and repair of tubular epithelial cells after AKI [22]. Only one percent of renal tubular cells in a male subject who received a kidney from a female donor included renal tubular epithelial cells with the Y chromosome. Using paracrine approaches rather than vasculature or tubular replacement, post-ischemic reduction, tubular epithelial cells, correction of renal microvasculature, and restoration of function after IRI was achieved by intravenous injection of bone marrow MSCs cells of the epithelium [22]. By directly inhibiting cell death and blocking the entrance of inflammatory cells, BMDCs may start to exacerbate the damage. Substances that encourage epithelial cell growth and proliferation are released by BMDCs during the repair phase [23]. Additionally, BMDCs contribute to glomerular regeneration. With similar regeneration abilities as BMDCs, ADMSCs are a desirable source of stem cells. Other cell types, including myocytes, adipocytes, neurons, and osteoblasts, may be differentiated by ADMSCs [21]. ADMSCs have the benefits of low harvest infiltration and high yielding from growth. These cells have no source of the behavioral problem and little concern about allo- and xenografting safety [24]. The most significant factor is that ADMSCs have stronger immunological and anti-inflammatory effects than BDMCs for renal fibrosis after damage by reducing the inflammatory response and oxidative stress [25].

III. METHODS OF RENAL REGENERATION

The nephron is a functioning kidney unit and there are about one million individual nephrons in adults. The proximal tubule, glomerulus, distal tubule, Henle loop, and collecting duct are crucial components of the nephron. There are several blood vessels all around the nephron as well [22]. Various kidney diseases lead to damage to various cell types like tubular epithelial cells, podocytes, endothelial, or mesangial cells. Although fatal injuries impair the function of the kidneys to varying degrees, they also affect the processes involved in regenerating damaged kidney tissue [22]. The four main pathways for kidney regeneration identified in the current study include renal cell regeneration, BMDC (bone marrow transplantation), macrophage infiltration into the kidney, and neoangiogenesis. There is considerable evidence that the regeneration process uses cell division like kidney development. Following adult kidney injury, vital genes during nephrogenesis may control tissue repair and cell regeneration [26]. Additionally, after kidney damage, BMDCs move to the kidneys where they may both enhance renal cell proliferation and inhibit renal apoptotic cells with an anti-inflammatory impact [27, 28].

Macrophages can feed dead tissue at a critical stage and promote the regeneration of tubal cells during extracellular tumors for repair [27]. The bloodstream may be used to attract renal progenitor cells, which can differentiate target cells, boost kidney cell proliferation, and help in renal regeneration following injury [21]. Vascular development and endothelial progenitor cells (EPCs) increase neoangiogenesis, which may lessen oxidative stress and prevent the loss of nephrons [29]. The mechanisms of kidney regeneration also include a large number of cells. Tubular epithelial cells may first divide and expand [26]. Humphreys et al. identified that internal tubular epithelial cells are a significant source of new cells in the healing of post-chemical nephron using mapping methods.

Second, growth factors like hepatocyte growth factor, IGF-1, and EGF (“Epidermal growth factor”) may be released by HGF (“Hepatocyte growth factor”), and such regeneration growth factors have a paracrine function to encourage regeneration by binding to receptors on proximal tubular epithelial cells [30]. Third, to encourage angiogenesis, remodeling, and the proliferation of epithelial cells, wound recovery or non-macrophages may generate a range of growth factors like Wnt7b. Furthermore, kidney function after injury may be significantly impacted by the integrity of the kidney's vascular system. Recent studies have shown that endothelial cells express the gene SCUBE1, which is necessary for the synthesis of a new protein. SCUBE1 inhibition may stop tubular epithelial cells from proliferating *in vitro* [31]. Normal renal pericytes are capable of stabilizing microcirculation. Although strong activation of pericyte/perivascular fibroblasts promotes kidney fibrosis, temporarily activating pericytes around the injured tubules can be a common remedy and facilitate effective recovery after AKI. The proliferation of kidney epithelial cells is encouraged by the production of cytokines by renal fibroblasts such as fibroblast growth factor-1 and -7, confirming the advantageous function of pericyte activation during renal healing after AKI.

Adult cells with significance for the stomach, bone marrow, skin, and intestines have long been recognized [25]. However, the abundant data that has been provided up to this point demonstrates that there are many cells, which regenerate the kidneys of adults. Regenerative cells may be seen in the condensed mesenchyme that surrounds the branching ureteric bud during renal development that can create all the other nephrons, interstitial, and vasculature cells in the first stage of the epithelial mesenchyme mutation. The distribution of the new nephron to humans was completed by the 36th week of pregnancy and continued for one to two weeks after the birth of the mouse. According to Hartman et al., condens mesenchyme stem cells eradicated asymmetry, self-renewal, and segregation before displaying an innate commitment to mesenchyme epithelial transition. Before the reproductive phase, the cells were depleted [25]. This shows that full regeneration, which involves completely removing the missing nephron, does not take place in mammal kidneys.

IV. ANGIOGENESIS AND RENAL REGENERATION

When repairing the kidneys and lowering renal dysfunction, particularly in CKD, vascular integrity is crucial. CKD, a major cause of gradual loss of renal microvasculature that results in tissue hypoxia and inflammation, further fibrotic alterations, and prone loss, may be caused by any number of etiologies. Tissue fibrosis has led to an abnormal rupture and this malignant cycle causes irreversible kidney function [22]. Proangiogenic and antiangiogenic cells are in balance in the normal range, but angiogenesis abnormalities are seen as CKD progression of Vascular endothelial factor, a proangiogenetic element that may improve kidney function and lessen fibrosis in the chronic renal failure state still present. IRI may be a factor in small vascular tilt, although the dysangiogenic isoform of vascular endothelial growth factor had a significant impact on fibrotic kidneys brought on by unilateral ureteral obstruction [30] medical genetics with the use of an adenoviral vector expressing angiopoietin-1, the diabetic nephropathy model has shown decreased albuminuria, suppression of mesangial expansion and podocyte damage linked to decreased macrophage infiltration and decreased chemokine and molecule adhesion. On the other hand, increased plasma levels of angiopoietin-2 have been linked to cardiovascular illness in CKD and may contribute to the development of CKD [22]. The role of these angiogenic growth factors in remodeling has to be further investigated. It has been shown that EPCs have a role in the regeneration of glomeruli and interstitium microvessels. Systemic injections of EPCs directed to sites of renal damage and injury improved kidney function decreased proteinuria, enhanced vascular strength and decreased apoptosis in mice with adriamycin-induced nephropathy [31]. The growth and restoration of the microvasculature is a crucial prospective target for the treatment of affected kidneys.

V. KIDNEY DISORDERS

Over 10% of the world's population suffers from the renal illness, which causes 5 to 10 million fatalities each year and is mostly attributable to the rising rates of diabetes, obesity, cardiovascular, and hypertension disease.

There are two types of ailments that affect the kidneys:

- 1) CKD
- 2) AKI

AKI is a prevalent clinical problem that affects between 15% and 50% of critically sick patients, and it is linked to both long- and short-term injury and even death. AKI is defined as the sudden failure of renal function and may have pre-renal (hypoperfusion), intra-renal (nephrotoxic substances), or post-renal (urinary tract blockage) causes. The proximal tubular cells' impairment which prevents them from producing enough energy, causes them to undergo apoptosis, detach, and clog the lumen, increasing intratubular pressure and causing "backleak" of filtrate, which contributes to dysfunction, is another characteristic of AKI. In parallel, vascular rarefaction is brought on by endothelial cell damage.

AKI appears clinically when there is a rapid rise in nitrogen metabolites and serum creatinine, which indicate a decline in GFR (“Glomerular filtration rate”), or a significant drop in urine output. Significant attempts are being undertaken to find biomarkers that may be utilized as early AKI predictors as shown by the delayed diagnosis of many AKI patients. Some of these included enzymes, indicators of changes in renal structure, and mediators of inflammation, such as neutrophil gelatinase-associated lipocalin and IL-8 (alanine aminopeptidase, and alkaline phosphates). An AKI's administration relies on its aetiology since, wherever feasible, the major reversible source of harm should be eliminated. Even when they don't aid in AKI recovery or lower mortality, nephrotoxic medications must be avoided and diuretic treatment and fluid resuscitation must be utilized to manage volume excess. Life-saving renal replacement treatment may also be necessary. Significant efforts are underway to find new targets for AKI management, like substances that affect hemodynamic, oxidative states, inflammatory, mitochondrial function, and cell metabolism.

CKD may be activated by a variety of risk factors, such as cardiovascular disease, diabetes, nephrectomy, and toxic exposures. About 18 percent of the world's population suffers from CKD. The kidney's structure and function continue to deteriorate over time in CKD, which is characterized by nephron loss, podocyte separation, glomerular hypertrophy, and the development of sclerotic lesions. Additionally, interstitial fibrosis and immune cell infiltration coexist with nephron atrophy.

There are few treatment options or methods to restore a badly injured or chronically ill kidney, and the condition is often diagnosed delayed because asymptomatic initial condition. Kidneys with severe damage might develop ESRD (“End-stage renal disease”) and kidney fibrosis. Renal replacement treatment, which includes kidney transplantation and tries to replace vital kidney function, is necessary for those with ESRD. Dialysis is not recognized as the best course of therapy because of the high expenses of care and detrimental effects on the subject's quality of life.

Since hypertension is acknowledged as one of the CKD causes, the treatment for CKD subjects now relies on the usage of medications for BP management and for inhibiting the renin-angiotensin-aldosterone pathway, which is essential for blood pressure regulation. The development of ESRD might be slowed down by beginning the rehabilitation process early.

There is a growing understanding that CKD and AKI are interconnected and probably contribute to one another. Although CKD is still one of the best predictors of acute renal damage, recent epidemiologic research has shown a complicated relationship between the two clinical entities. However, it is clear that there is a bidirectional association between AKI and CKD, wherein having CKD raises the chance of developing AKI.

VI. EXPERIMENTAL EXAMPLE

Morrison et al. have reported a protocol for differentiating hPSCs (“Human pluripotent stem cells”) into multiple NPSCs (“Nephron progenitor cells”) that can give rise to a nephron-like structure. In both two- and three-dimensional cultures, NPSCs can develop kidney organoids that have epithelial nephron-like structures that express markers for the proximal tubules, loop of Henle, and distal tubules of podocytes [32]. Lee Et al. conducted a study in which the transplanted induced pluripotent stem cells (iPSCs) showed improved renal function and reduced death rate linked with AKI. iPSCs have anti-oxidant, anti-inflammatory, and antiapoptotic properties so; the transplantation of such cells is a treatment option for ischemic AKI [32]. Numerous researchers are also using the concepts of developmental biology in their work on the cellular method. Metanephric tissue, an embryological precursor of the adult kidney, can be successfully differentiated and developed into a functional nephron. Whereas Roger et al. successfully transplanted porcine metanephron into adult pigs and mice. Despite the fact that xenotransplantation needed further co-stimulatory blockade administration, such as anti-CD154, anti-CDR45RB, and anti-CD11b [33]. Also, Dekel et al. Showed the successful xenotransplant of human metanephron into immune-deficient mice. Observing similar gene expression patterns like human kidney development. Cells from the metanephric mesenchyme progenitor tissues and the wolffian duct/ureteric bud have been grown in vivo in both single and Co-cultures by Rosines et al. To get kidney important structure, renal bioengineering was performed using a developmental biology technique, and they grew them on extracellular matrix gel to reconstitute 3D structure [33]. Successful in vivo organoid culture from single embryonic cell suspension, when implanted into rodents, organoid formed functional and vascularized glomerular and fully differentiated capillary walls, which showed tubular absorption function [33]. Shen et al. investigated how hiPSCs differentiated into iEPCs (endothelial progenitor cells), the iEPCs were introduced into the injured kidney and replaced in endothelial cells and cured AKI mice. The excellent work by Lee et al. identified mouse kidney progenitor cells that can develop into tubular epithelial and endothelial cells from the interstitium of the papilla and medulla. After ischemia damage, mouse kidney progenitor cells treatment may lower the death rate [28].

For ESRD subjects on dialysis and in need of kidney transplants, bioengineered kidneys are crucial. Earlier studies developed hemofiltration devices using bioengineered renal tubules that may temporarily restore renal function in individuals with acute failure of renal and replace renal function in uremic dogs.

A bioengineered kidney with a design and function that allows for urine perfusion, secretion, filtration, drainage, and absorption is still being researched. Through the use of detergent perfusion, they were able to decellularize rat cadaveric kidneys, producing acellular scaffolds with cortical, vascular, and medullary architecture, ureters, and collecting systems. The endothelial and epithelial cells were then transplanted into rat kidney scaffolds. Organ cultures of regenerated kidneys produced urine *in vitro* after a few days. An orthotopic location allowed for the recipient's circulatory system to perfuse and generate urine *in vivo* when the transplants were placed there. It's nevertheless an important milestone in the field of kidney regeneration medicine, even if a regenerated kidney can only provide partial renal function [34, 35].

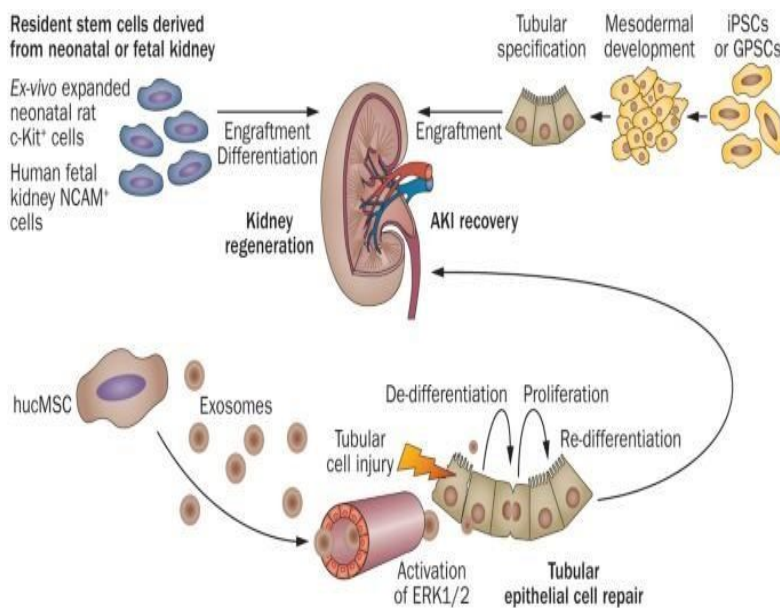


Fig. 2 Flow diagram of Kidney regeneration and AKI recovery

VII. CHALLENGES IN CLINICAL STEM CELL THERAPY

It is an excellent and effective alternative treatment to current therapies because this can provide a cure for kidney diseases and injuries without a transplant or dialysis. Stem cell therapy can be considered for the repair and regeneration of kidney tissue. For stem cell treatment to be used clinically, several challenging concerns must be addressed.

Stem cell therapy's clinical effectiveness depends on a variety of factors, including the optimal selection of cell types and the volume of cells processed which is needed to be resolved. Because of ethical reasons pluripotency tests, which need to be performed on hiPSCs cannot be done, which affects the result of treatment.[3] For the regeneration of any organ by stem cell therapy the microenvironment is one of the important factors which influences the whole regeneration process. It either prospers the regeneration process because of the appropriate microenvironment or it me also produces hurdles in the growth of the stem cells.[3] Tumorigenicity is one of the important challenges faced in stem cell therapy especially, iPSCs are extremely proliferative owing to the use of viral vectors for reprogramming iPSCs, there is a high chance of tumor formation, after the transplantation. Certain securer alternatives like using small compounds, are either less effective or do not induce pluripotency on their own [36]. Stem cell therapy shows promising results in, *in-vitro* conditions but, low engraftment, lower survival, and decreased paracrine ability of implanted cells *in vivo* limit the effectiveness of therapeutic studies. Immune rejection of stem cells is another major challenge, stem cells like hESCs, against which a strong immune response is generated by the host body. iPSCs show some hope because they have the same genetic background that's why they can be tolerated by the human immune system [36]. Stem cell therapy's therapeutic effect depends on the correct selection of cell types, the cell numbers needed to treat, and the method of administration. These factors, taken collectively, determine the treatment's outcomes and effectiveness, and they may be implemented into clinical practice soon [37]. In experiments, cell numbers might vary depending on the kind of stem cells employed and how they are utilized. Cell quality and downstream processing are other issues which are needed to be resolved. Because of ethical reasons pluripotency tests have been done which affect the result of treatment [37].

VIII. CONCLUSION

In this review article, we summarized some recent advances for repairing kidney damage using the stem cell approach. A more compelling pre-clinical model of stem cell effectiveness in treating renal disease is still lacking. It's still a priority to find the best source of kidney cells for *de novo* regeneration. A better knowledge of stem cell behavior would allow researchers to find the ideal cellular source, mode of application, and optimal dosage for diverse kidney disorders. It is hoped that organ regeneration utilizing stem cells in bigger animals would make it easier to create large organs for human transplantation, helping to alleviate the scarcity of organ donors.

IX. ACKNOWLEDGMENT

I am highly obliged to the team EDU FABRICA and Indian Institute of Technology, Kharagpur, for helping me with the proper guidance and encouraging me to write this paper. My colleagues Anjali Majhi, Ketaki Rajwade, Khushi Chaturvedi, Kshanaprava Mohanta and Pranali Joshi; who supported me to an extent in providing procedures of writing paper and with the content. This is my first paper, so I am highly elated to share and hope the information provided here will genuinely be helpful.

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