Stem cell as an option for kidney Injury and Transplantation

By

Faizul Kabir
18146056

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

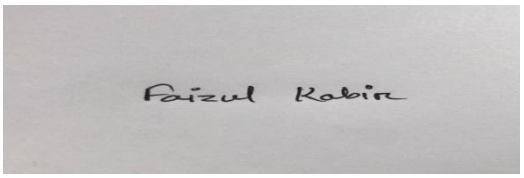
School of Pharmacy
Brac University
August 2022

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:



Faizul Kabir
18146056

Approval

Deputy Chair

Dr. Hasina Yasmin Professor
Professor, Assistant Dean
School of Pharmacy
Brac University

Departmental Head:
(Chair & Dean)

Dr. Eva Rahman Kabir
Professor & Dean,
School of Pharmacy
Brac University

Supervisor:
(member)

Dr. Afrina Afrose
Assistant Professor, School of Pharmacy
Brac University

The thesis/project titled "Stem cell as an option for kidney Injury and Transplantation" submitted by Faizul Kabir (18146056) of Spring, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 30/08/2022.

Ethics Statement

No living organisms were harmed during this project.

Abstract

In the past few years, kidney disease has become a major health problem all over the world. These diseases affect more than 10% of the world's people and are getting worse all the time. Chronic kidney disease (CKD) is becoming more common in the United States at a rate of 6-8% per year. Dialysis and transplantation are the only treatments available at this time. But it’s limited due to lack of donor. Therefore, finding new and better treatments for kidney diseases is essential for enhancing patient survival and quality of life. However, Stem cell [SC] therapy and regenerative medicine may bring new choices for renal disease. These potential treatments might include employing endogenous or external stem cells to repair or reprogram the organ to renew. This study will focus on stem cell-based therapies for kidney illnesses, including cell sources, mechanisms, consequences and future issues also the risks in clinical use.

Keywords:

Mesenchymal stem cell, Stem Cell Therapy, Chronic Kidney Disease, Renal stem/progenitor cells,

Dedication

Dedicated to my parents

Acknowledgement

First and foremost, I am thankful to Allah for allowing me to pick this subject and pursue my study on Pharmacy. Without His mighty blessings, I would be unable to complete this project to submit it in order to get my Bachelor's degree in Pharmacy.

This work would not have been possible without the assistance of many persons, all of whom are respectfully recognized here. First of all, I would like to express my heartfelt gratitude to my honorable supervisor, Dr. Afrina Afrose (Assistant Professor, School of Pharmacy, Brac University), without whom I would not have had the opportunity to study over such a fascinating topic. Because of her consistent effort and inspiration for my work, I was able to work more diligently. Her words have inspired me to enhance my capacity to communicate ideas effectively. While supervising, she consistently and eloquently exhibited her utmost sincerity, which motivated me even more to accomplish this project. I'd like to sincerely thank our respected Eva Rahman Kabir (Professor and Dean, School of Pharmacy) and Dr. Hasina Yasmin (Professor, Assistant Dean, School of Pharmacy) for their assistance during my whole journey.

I am also appreciative to the teaching assistants at Brac University's Department of Pharmacy for their time and assistance whenever I needed of it.

Finally, I'd like to express my heartfelt gratitude for their unwavering support and encouragement throughout my life. They give me the motivation and fortitude to work vigilantly and more patiently. Their constant prayers and unconditional love have helped me go this far.

I respectfully express my gratitude to everyone who assisted me in this project.

Table of Contents

List of Figures

List of Acronyms

CKD = Chronic Kidney Disease

SC = Stem cell

Esc = Embryonic Stem cell

iPSCs = Induced pluripotent stem cell

RPCs = Renal stem/progenitor cells

Msc = Mesenchymal stem cell

SSCs =somatic stem cells

GScs = Germ line stem cells

Chapter 1

Introduction

1.1 Background

Kidney diseases have increased and since then becoming a global health concern. Renal failure (CKD) is rising globally, although the U.S. rate is 6-8% per year. More elderly individuals and diseases including diabetes, heart disease, and high blood pressure create more of these conditions than 10% of the world's population. Kidney failure, whose symptoms are caused by decreasing kidney function, is still the worst outcome of CKD, even though high serum excretion-adjusted combination therapy can prevent chronic nephropathies. End-stage renal failure patients have two options: dialysis or a kidney transplant, but there aren't enough donors and the body may reject it. Stem cells and regenerative medicine may soon change that. Reprogramming an organ to start developing anew or employing endogenous or exogenous stem cells can help it repair or grow again. Several cell-based therapies could help restore kidney function and treat renal failure. Unhealthy kidneys can be treated using stem cells. Success depends on how well SCs can differentiate, organize, and integrate into existing tissues to restore function, as well as create Reno protective factor.

1.2 Research Gap

In the analysis of alternatives for kidney injury and transplantation, stem cells and regenerative medicine are already being introduced as an alternative to dialysis or kidney transplantation. This is due to the quality of stem cells. Stem cells are a type of cell that has the ability to self-renew and it can develop into a diversity of adult cells. This systemic review looks at the various stem cell treatment options for kidney injury and transplantation, and also which one is the best.

1.3 Objective

The aim of the article is to review the merits and disadvantages of stem cell transplant for renal failure. To achieve the purpose our research will complete the following objectives.

Objective 1: To evaluate stem cell therapy as a therapeutic approach for kidney disease.

Objective 2: To outline the mechanisms of stem cell treatments aid to recover kidney function.

Objective 3: To justify that the Mesenchymal stem cell [MSC] is the ideal option for kidney cell treatments.

Overall, the goal of this study is to establish that stem cell therapy is one of the most effective remedies for kidney problems and donation.

1.4 Significance

By evaluating the medical decisions for kidney injury and transplantation, this study may assist in the development of plans of stem cell therapy treatment options for renal illness and failure, as well as the discovery of the best candidate stem cells. Stem cell therapy would provide a new method of reaching successful results in kidneys by lowering the side effects or negative effects of available therapeutic choices. In that situation, stem cell therapy may be the most successful therapy for renal impairment.

Chapter 2

Methodology

This article provides a comprehensive summary of several treatment options Kidney diseases and failure through stem cell therapy and regenerative medicine and the best stem cell option for the treatment. Information for this review paper was gathered from peer-reviewed published studies, news items, academic published papers, and web sites. Furthermore, for this study, articles from prestigious journals such as Springer, Nature, Cells, The Lancet, MDPI, Frontiers, Bio pharma, Taylor and Francis were evaluated. Many articles were consulted for information and data, which aided in determining the importance and future of stem cell as an option for kidney diseases and failure. All of the information was collated and properly referenced, resulting in a greater understanding. Attempts were made to discover gaps or withholding data in the available literature. The majority of this research focuses on the stem cell options for the treatment of kidney diseases and transplantation such as Esc, Msc, iPSCs etc. Self-renewal is the crucial component of stem cells which is used mainly in all the options for availing the treatment. It implies that the organism's ability to multiply and self-renew for at least one natural life span has not been compromised. (LAJTHA, 1979). Numerous studies indicate that Stem cells would repair or increase the function of destroyed renal cells in a unique cell-based therapy for renal diseases (Mae et al., 2013c). However, among all researches MSC became the best treatment option for kidney injury and transplantation because of its sourcing, availability and useful amplification.

Chapter 3

Stem Cell

Stem cells can proliferate and become numerous types of adult cells. Embryonic organogenesis and tissue regeneration depend on these features. In recent years, several scientists have studied stem cells. Embryology, hematology, neurology, and skeletal biology benefit from stem cell research. Stem cells are tissue cells that can maintain their number, function, and size while also sending out daughters to generate new functioning cells. If the daughters want a working government, they must get older or more talented (LAJTHA, 1979).

In recent years, several scientists have studied stem cells. Embryology, hematology, neurology, and skeletal biology have profited from stem cell research. Stem cells may self-renew, transform into different cells, and generate more of the same sort. Daughters may require longer time to mature and/or change. Even if stem cells die, they can proliferate (maintain). It signifies the organism has reproduced and grown for at least one generation (LAJTHA, 1979).

Stem cells can divide into adult cells indefinitely. These qualities are necessary for embryonic organ development and tissue healing. Experts from several sectors have worked on stem cell research in recent years. Embryology, hematology, neurology, and skeletal biology gain from stem cell research. Stem cells are tissue cells that maintain their number, function, and size while sending forth daughters to generate new functioning cells. Girls require greater distinction and/or maturity to operate completely (Scadden & Srivastava, 2012).

Embryonic and adult stem cells can become cancerous. The blastocyst's core cell mass gives birth to pluripotent embryonic stem cells, which can form all three germ layers. Embryos create GSCs for reproduction and SSCs for organ development (Lajtha & Oliver, 1962).

3.1 Recent statistics

Kidney ailments have become a global epidemic due to their continually rising occurrence. Key etiologies such as diabetes, cardiovascular disease, and hypertension are on the rise as the world's population ages (Jager & Fraser, 2017). Over 10% of the country's individual affected by these disorders. Kidney disorders covers a large variety of illnesses that impair the structure and function of the kidneys, as well as a wide range of clinical features and consequences. The length of kidney disease affects whether it is acute or chronic. Chronic renal disease is increasing significantly of 6–8% each year in the United States alone.

With age, the prevalence of CKD grows, reaching 20% in those over 60 and 35% in those over 70. To truly understand the potential of cellular treatments or regenerative treatment for the kidney, one must first appreciate normal renal growth and harm response. The kidney was once thought to have limited cell turnover and no powerplant. The idea remains, however, that the kidney develops a maximum nephron complement and thereafter loses them. Our comprehension of how this organ develops has led us to this assumption.

3.2 Potential sources

Stem cell-based regenerative therapy shows promise for addressing degenerative disorders. Stem cells would repair damaged kidney cells in a novel cell-based therapy for renal diseases. Injury-caused renal failure requires cells to grow into injured tubules and become renal tissues. Adult bone marrow stem cells can become kidney resident cells and repair the organ (Mae et al., 2013c). (2008) (Humphreys et al., 2008). Several SC subsets have been studied to repair injured kidneys. PSC-based renal tissue engineering has gained popularity swiftly.

Ethical and allogenic mismatch constraints prevent clinical usage of embryonic stem cells. Pluripotent ESCs may develop any type of kidney cell making them the best candidate. Mae et al. helped ESCs grow into intermediate mesoderm (Mae et al., 2013). ESC-derived renal

cells can be converted into glomeruli and injected into the kidney's proximal tubules to restore kidney function in animal models (Vigneau and colleagues, 2007). Mae et al. This sort of cell can't be utilized as much as it might be morally because to teratomas and immunological rejection. Pluripotent stem cells are embryonic and induced (iPSCs). Stem cells can become adipocytes, chondrocytes, and osteocytes (Imberti et al., 2015). Fat tissue, bone marrow stroma, and umbilical cord blood contain MSCs. MSCs grow easily to therapeutic sizes (Prockop, 1997) (Li & Ikehara, 2013). These cells can repair damaged tissues and organs.

3.2.1Embryonic stem cells

The inner cell mass of the blastocyst generates ES cells, but their use is hampered by scientific, legal, and moral implications. ESCs' self-renewability and multiline age differentiation are two characteristics that look promising in kidney regeneration and cell therapy. Several studies have revealed that mouse ESCs can merge into kidney compartments, suggesting that they could be beneficial for kidney repair. In addition, molecules needed to identify kidney, such as activin A, retinoic acid, and bone morphogenic proteins (BMPs), promote in vitro differentiation of ESCs into renal lineage cells (Narayanan et al., 2013) (Takahashi & Yamanaka, 2006). Yamamoto et al observed that teratomas can be generated in vivo by introducing pluripotent cells (Yamamoto et al., 2006). They developed teratomas with metanephric–mesenchyme-like structures after infusing undifferentiated embryonic stem cells into the peritoneum membrane of nude mice (Steenhard and colleagues, 2005). Steenhard et al. showed that 50% of ESC may be absorbed into embryonic kidney tubules without inducing teratoma formation. To mature into renal progenitor cells, ESCs were stimulated with acitivin-A, BMP7, and retinoic acid (Kim & Dressler, 2005). This resulted in the production of intermediate mesoderm and kidney development markers. Renal replacement therapy is recommended for patients with ESRD. Dialysis, on the other hand, is

just a brief treatment for patients. Renal hemostatic and endocrine failure, as well as its complications, are not addressed with dialysis (Wolfe et al., 1999). However, the desire for donor organs has exceeded the supply (Garcia-Garcia et al., 2012). Because of its precise shape and sophisticated structure, the kidney is one of the hardest organs to regenerate. Many ways have utilized ESC differentiation to create complex kidney-like structures known as organoids, which can arrange themself and comprise various kinds of renal cells.

3.2.2 Bone marrow-derived cells

HSCs and MSCs, which act as stromal support for HSCs, are two types of stem cells found in bone marrow (BM). One of the most well-known sources of stem cells, bone marrow, has long been regarded to aid in the repairing of many other organs (Wagers & Weissman, 2004). Previously research found in kidney, bone marrow-derived cells using gender miss matched donors and recipients (Poulsom et al., 2001). The capability of bone marrow to home to renal tissue has been firmly linked to kidney tissue injury, having no proof that it occurs without renal tissue damage (Lin & Igarashi, 2003). Despite traces of cells incorporating into several cellular compartments of kidney, the extent of engraftment and functional trans differentiation were studied more carefully.

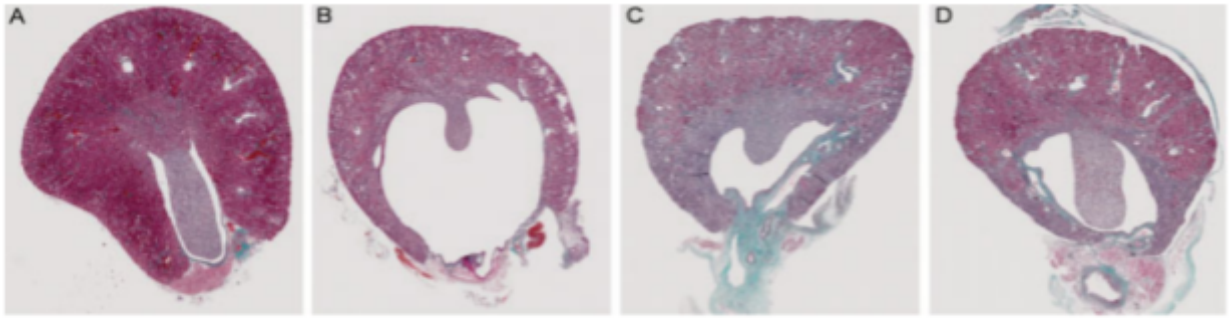


Figure : staining sections of contralateral kidney. A) Normal histology of unobstructed kidney B) 7 days of obstruction C)replacement of renal medulla after reversal D) Restoration of renal parenchyma after 2 week. (Hopkins et al., 2009)

Additionally, Held et al shown that chronic renal destruction might cause a 20–50% cell fusion of renal tubular cells and bone marrow-derived cells. In a glomerulonephritis mice

model, BMM cells in the renal arteries accelerated kidney regeneration after being transplanted into the renal artery. Due to both endothelial cell absorption and angiogenic factor production. Activating BM stem cells using m-CSF, G-CSF and SCF may also improve kidney regeneration (Nishida et al., 2004) (Stokman et al., 2005). Almost all of these studies indicated that growth factor treatment improves kidney function following ischemic or toxic impairment. Proliferation, apoptosis, and neutrophil infiltration are related to this improvement, the scientists said. Not all consequences are positive. Unfractionated male BM cells implantation which are non-functional into female recipient proximal tubules, distal tubules, thick ascending limbs, and collecting ducts (Hopkins et al., 2009).

3.2.3 Induced pluripotent stem cell

Alternative cell sources for ESCs comprise the induced pluripotent stem cells (iPSCs), that have the same kind of properties to regenerate as Embryonic Stem Cells. iPSCs may keep both the genetic history and the origin of cell's specific epigenetic memory in the therapy of cell, the regeneration of kidney, as well as different biomedical activities, providing indisputable benefits (Liu et al., 2020).

Induced pluripotent stem cells, which may be collected from humans and delivered as a treatment for the kidney replacement without the suppression of immune system, are the most powerful source for creating regenerated kidney tissues for implantation (Becherucci et al., 2018). The human iPSCs have been created from a range of sources, comprising keratinocytes, skin fibroblasts. Peripheral blood cells, cord blood, hepatocytes, stomach cells, extra embryonic tissues, completely differentiated T and B cells and, dental pulp (Takasato et al., 2015). The pluripotency of terminally differentiated renal cells is reprogrammed. In regards of structure and gene expression, kidney-derived iPSCs are close to human ESC form of colonies (Zhou et al., 2011) (Dai et al., 2015).

Human kidney proximal tubular cells were used to produce iPSCs. iPSCs can also be obtained from micro porous tubular cells of kidney found in urine, which is an easy and non-invasive process (Zhou et al., 2011). iPSCs may retain both epigenetic and genetic memory of their cells of origin, which could be useful for the regeneration of kidneys, cell therapy and other medicinal applications (Dai et al., 2015).

The key mechanism by which generated pluripotent stem cells relieve kidney tissue damage in CKD and AKI might be through the pathways of paracrine. Recently reported that iPSC-derived extracellular vesicles reduced macrophage infiltration, protected mitochondria, and altered oxidative stress genes, improving Reno protection in AKI animals (Collino et al., 2020). In the trial by Lee et al., iPSC transplantation restored renal function and lowered AKI mortality, showing antioxidative stress, anti-inflammatory, and anti-apoptotic effects. High dosages of iPSC accumulation may cause renal impairment. High dosages of iPSC accumulation may trigger kidney damage. Because PSCs are undifferentiated, there is a substantial danger of maldifferentiation and ultimately tumor growth when delivered without pre-differentiation. Gene editing techniques like CRISPR/Cas9 have recently made it feasible to cure genetic kidney illnesses by changing an iPSC line (Becherucci et al., 2018) (Takasato et al., 2015).

3.2.4 Mesenchymal stem/stromal cells

One of the most sophisticated SC-based therapies evaluated in people is MSC-based medication. MSCs can be grown in a lab, thus a single source can yield several therapeutic dosages. MSCs are excellent for allogeneic off-the-shelf therapy since they lack CD40, CD80, CD86, DR antigens, and blood type (Horwitz et al., 2002). Multipotent, able to stay together in culture, displaying conventional surface markers (CD73, CD90, and CD105), and not expressing hematopoietic lineage markers (CD11 or CD14, CD19, CD34, CD45, CD79a, and human leukocyte antigen class-II) (Dominici et al., 2006). Stem cells can be extracted

from the kidney or bone marrow stroma. MSCs are easy to develop and can become many medical cells. MSCs are used to treat organ problems because they may go to places affected by ischemia, hypoxia, or inflammation. MSCs are directed to tissue-damaged areas because they have chemokine receptors (Herrera et al., 2007). For MSCs to migrate, CXCR4/SDF-1 must operate effectively. CXCR4 overexpression helps BMMSC restore renal function after AKI (Liu et al., 2013).

Intravenous MSCs improved kidney shape and function. MSCs developed on the tubule epithelial lining when injected into the damaged kidney. In some investigations, renal MSC engraftment was restricted and short-lived, even though MSCs may engraft into damaged kidney sites following a transplant (Kale et al., 2003).

Chapter 4

Discussion

A number of regenerative cell-based remedies for renal failure are getting investigated. The first therapy is a stem cell injection immediately into the affected kidney. The ability of SCs to identify, arrange, and integrate into preexisting tissues in order to reestablish function, as well as their ability to generate Reno protective compounds, is crucial to the treatment's therapeutic success. Adult SCs and other types of progenitor cells, such as renal progenitor cells, endothelial progenitor cells, and bone marrow MSCs, have all been investigated in kidney damage models. Similarly, ESCs and iPSCs have recently been explored. Despite the fact that several clinical trials advise that MSCs be provided to CKD patients because it is possible and acceptable, the actual value of those cells is unknown, and numerous essential problems, such as cell type selection, route of action, and delivery timing, must be solved. MSCs for SC-based renal damage treatment are suitable of their own group (S. A. Lin et al., 2010).

4.1 MSCs

Many types of stem cells have already been investigated for their ability to repair injured kidneys, with the rare occurrence that the ideal cell type for renal regeneration is still being discussed.

Pluripotent ESCs can become any type of kidney cell. Because they may convert into numerous types of cells, transplanted cells are more prone to produce neoplasms, which is a concern. Activin A, retinoic acid, and bone morphogenic proteins enable ESC become renal progenitor cells. This reduces danger (Bruce et al., 2007) (Vigneau et al., 2007).When firms can't stand out, few grow. This sort of cell might be rejected by the immune system or grow into a teratoma, and there are ethical considerations.

Due of their young, undifferentiated iPSCs raise safety issues after transplantation. iPSCs may be differentiated into nephrogenic cells and podocytes from renal proximal tubular cells (S. A. Lin et al., 2010) (Takasato et al., 2013). No AKI animal models have shown that pre-differentiated iPSCs enhance kidney function or tissue engraftment. After 4 days and 8 weeks of injecting iPSC-produced RPCs into renal tissues, there were no symptoms of improper differentiation or oncogenicity (Imberti and colleagues, 2015b).

MSCs are employed to repair renal damage caused by SCs. Stem cells may be extracted from bone marrow stroma (Dominici et al., 2006b) (Meirelles et al., 2006). Growing MSCs to therapeutic levels. MSCs can form osteocytes, chondrocytes, and adipocytes. MSCs affect the immune system. They're the most promising cells for treating damaged tissues and organs. They are associated to mesenchymal stem cell (MSC) migration, which is regulated by the SCF1/CXCR4 axis, a stromal cell-derived factor, and to MSC transformation into kidney-specific cells (Morigi, 2004). Herrera et al. After the embryo and kidney had grown for a period, MSCs were injected directly into the developing glomerulus, tubules, and interstitium. MSCs can be injected directly into the kidney (Yokoo et al., 2006). Some findings demonstrate that MSCs do not cure the kidneys by repopulating and engrafting tubules.

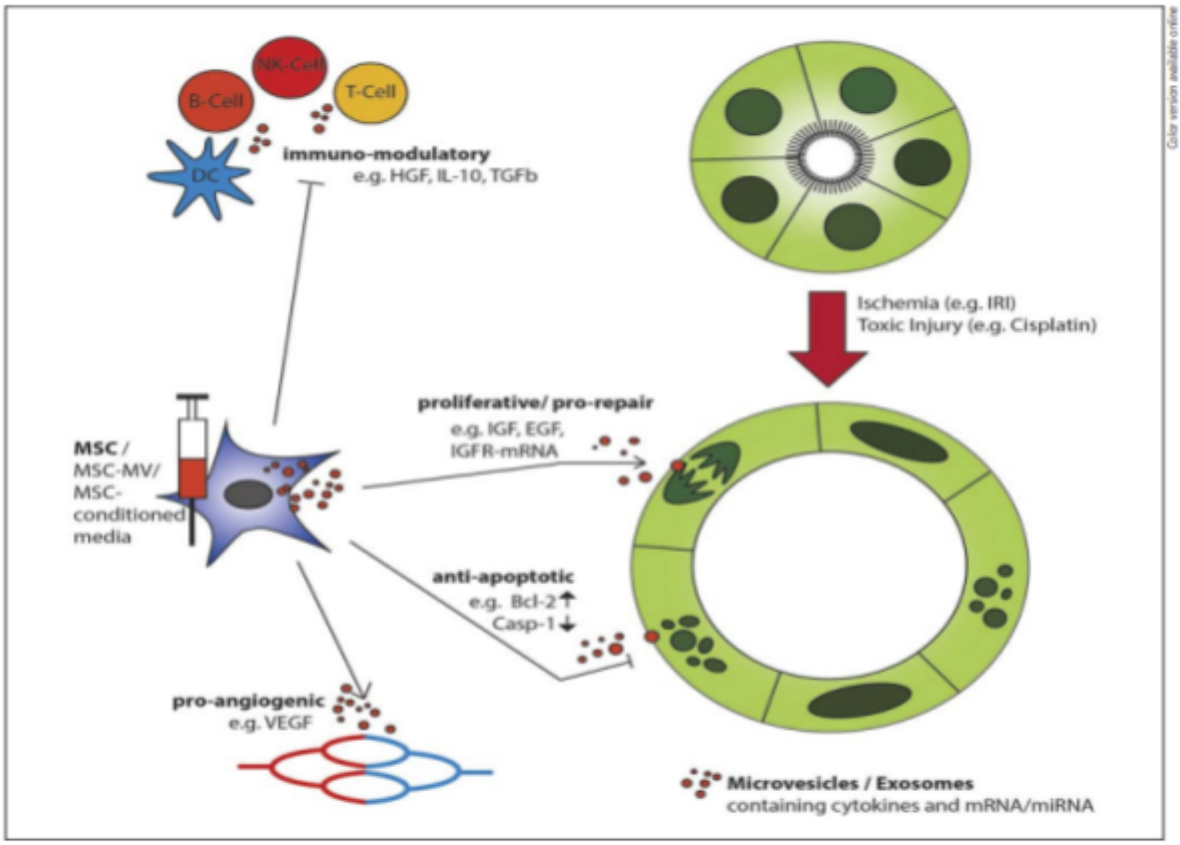


Figure : Paracrine actions of Msc on the injured tubules and surrounding tissue (Fleig & Humphreys, 2014).

Tubular cell proliferation and apoptosis delay regeneration. Injecting MSC, MSC-MV, or MSC conditioned media increases tubular cell proliferation and limits apoptosis, boosts vascular development, reduces inflammation, and adjusts immunogenicity. Good effects of injected MSCs are generally obvious within 24 to 48 hours, which is too quick to explain by epithelialization (Humphreys & Bonventre, 2008). Second, MSC doesn't make enough epithelial cells to restore nephrons (Humphreys & Bonventre, 2008). Endocrine and paracrine mechanisms are associated to MSCs' kidney-protective actions. Patients with acute kidney I/R injury who received IV nestin+ MSCs agree. Nestin+-derived medium may prevent

ischemic kidney failure via VEGF. This treatment lowered apoptosis, serum creatinine, and BUN (Jiang et al., 2015).

MSCs generate growth factors and cytokines. Leukemia inhibitory factor, SC factor, G-CSF, monocyte-chemoattractant protein-1, IL-6, and IL-11, macrophage-colony stimulating factor, primary fibroblast growth factor, hepatocyte growth factor, and insulin-like growth factor-1 are well-known (Weimar et al., 1998). Some substances promote epithelial cell proliferation, while others protect blood vessels (Togel et al., 2007). Several anti-inflammatory and anti-apoptotic processes protect the kidney and promote recovery.

4.2 Renal stem/progenitor cells

Nephrogenic embryonic renal SCs are found to lower shortly after pregnancy or weeks before birth. At least 6000 cells from several nephron segments are lost in the urine per hour, emphasizing the significance of progenitor cells in restoring cells lost due to physiological processes (Mcmahon, 2005). Adult kidneys have been shown to survive acute and chronic injury, as well as to undergo structural remodeling or repair in a multitude of studies, suggesting that they may heal. These qualities have attracted attention in renal stem/progenitor cells in the area (RSPCs).

SC marker expression studies that included embryonic renal marker PAX2 and CD133+ cells were used to discover RSPCs in the medullary papilla area, distal tubules, and Bowman capsule of human kidneys (Aggarwal et al., 2016). In mature human kidney tissue, CD133+ renal stem cells relative effects CD24 Romagnani & Remuzzi, 2014). In Bowman's capsule, CD24+CD133+ cells with pluripotent differentiation potential and self-renewability were employed to fabricate a subpopulation of parietal epithelial cells (PECs) that expressed SC-specific transcription factors Oct-4 and BmI-1 (Sagrinati et al., 2006).

Adult RSPCs of multiple kinds and origins were revealed to have a therapeutic effect in rats and mice with tubular and glomerular degeneration. On the basis of reno protective molecules, RSPCs participating in kidney repair are related to the paracrine system. The activated RSPCs would regenerate the compromised kidney cells (Sagrinati et al., 2006).

4.3 Human clinical Trial

People are looking for new drugs. On-pump cardiac surgery patients at high risk of AKI were given extremely modest dosages of allogeneic MSCs in a Phase I research (NCT00733876). Togel and Westenfelder (2010) saw 5 patients. Their kidneys operated for 16 months without dialysis. Togel and Westenfelder (2010) discovered no negative effects to treatment. The research lowered hospital stays and readmissions by 40%. A Phase I trial demonstrated that autologous ex vivo-expanded MSCs given IV improved kidney function (NCT 01275612). In NCT 01602328, patients with sustained decompensation (creatinine rise of more than 0.5 mg/dl) after 48 hours of surgery were given human MSCs. The 2014 research "Sodium Bicarbonate Infusion to Reduce Cardiac Surgery-Associated Acute Kidney Injury" didn't discover satisfactory outcomes. Specific and early biomarkers may be better at predicting AKI and receiving medical care sooner, which raises the possibility of a positive result. Early study reveals MSC treatment is well tolerated, but more is needed to determine its effectiveness. Also, clinical trial outcomes must be examined to discover if adverse data originated from poorly set-up investigations (F. E. Togel & Westenfelder, 2012).

Chapter 5

Current Treatment Option

Corticosteroids and renin-angiotensin system inhibitors, notably ACE inhibitors and ARBs, are effective CKD medication therapies. Accelerating RPC differentiation helped adult mice and rats rebuild their glomeruli (Zhang et al., 2013) (Macconi et al., 2009). In non-diabetic and diabetic nephropathy animal models, therapy associated with ACEis and ARBs, hastened the cure of glomerulosclerosis and vascular diseases along with reducing subsequent kidney damage in combination or alone (Benigni et al., 2010). This reveals that having a lot of podocytes per capillary tuft might help alleviate the symptoms of ACE inhibitors (Macconi et al., 2009). Interestingly, ACEi therapy inhibited the development of glomerulosclerosis by suppressing PEC proliferation in crescent formation, indicating that this therapy can restore normal glomerular function (Benigni et al., 2011). AT1 (Ang II receptor) expression thought to be responsible for RPC proliferation (Rizzo et al., 2013). The data back up the significance of the Ang II/AT1 receptor network in driving incorrect RPC proliferation and migration in cell proliferation (Rizzo et al., 2013) (Zhang et al., 2013) and explain whether ARBs are efficient. The methods by which treatments slow the progression of renal dysfunction are still being investigated (Remuzzi, 2006).

Chapter 6

Future Aspects

SC therapy could be a potential way to treat kidney disease. MSCs are a favorable cell type because of their potential for allogeneic transplantation, ability to differentiate in vivo renally, and paracrine mechanisms of action, that have been established in several animal research. MSCs may gain from preconditioning or genetic manipulation to enhance engraftment, migration, survival, and paracrine capabilities (S. A. Lin et al., 2010). The donor's age, as well as the functional abnormalities of MSCs obtained from patients suffering from renal diseases is significant factors. The outcomes of longer, guideline to ensure, and methodically conducted clinical trials to test the concerns of malignancy and fibrosis will indicate the actual therapeutic effects of MSC treatment in renal diseases. In diagnostic trials, MSC injection had no obvious bad impacts. Because of variation in approaches such as the proportion of released cells and the timing of administration, the efficacy of these cells is up for discussion (Rizzo et al., 2013).

A tissue-specific progenitor cell, in our viewpoint, is the greatest source for curing tissue-specific conditions. This type of cell can be created from ESCs or iPSCs. The use of ESCs and iPSCs for kidney regeneration is still in its early phases of a project. Step-by-step differentiation protocols must be established to push pluripotent SCs to develop renal progenitors, intermediate mesoderm, and finally mature, functioning renal cells (Macconi et al., 2009).

Progenitor cells or adult kidney-specific stem cells will be used to heal chronic conditions. However, for the current being, these cells are unable to be used for any purpose based on a variety of factors. Furthermore, CKD or age might disrupt and limit the power of autologous

RPCs to replenish. RPCs are unable to completely replace lost cells, so many multiply and move at random, producing in lesions and sclerosis. Medicines or pharmaceuticals which target other suspected Reno protective mechanisms, as with chemokine receptor antagonists, may assist RPCs repair themselves and grow. Other signaling pathways involved in RPC maintenance, control, and damage response will definitely be revealed in the future (Dominici et al., 2006b).

Chapter 7

Limitations

Stem cell therapy appears to advance quickly, demonstrating some basic principles of kidney regeneration biology. The positive effects of this type of therapy could be maximized by increasing MSCs' migration, engraftment, survival, and paracrine actions through preconditioning or genetic modification techniques. But there is lack of techniques and expertise which is a major concern for this up growing research (Mias et al., 2008). The infusion of MSCs has not been linked to any significant negative effects in clinical trials (Tögel & Westenfelder, 2010).The effectiveness of these cells is still debatable, though, at least in part because of variations in the protocols utilized, such as the quantity of cells provided and the timing of administration (Tögel & Westenfelder, 2012). Donor age and the functional abnormalities of MSCs isolated from patients with renal disorders are additional crucial factors that may have an impact on the therapeutic potential of MSCs. Moreover,To confirm the long-term safety of these treatments, it is also necessary to conduct fully structured research works. In order to address the present issues with these cell types, continuous work is required to construct step-by-step differentiation methods that lead the SCs to first form intermediate mesoderm, then renal progenitors, and finally to become full, functioning renal cells (Mias et al., 2008b) .

7.1 Scope for Improvement

Stem cells have already been investigated for their ability to repair injured kidneys, with the rare occurrence that the ideal cell type for renal regeneration is still being discussed. Among from the options as MSC became the promising cell type because of its sourcing, availability and useful amplification. The positive effects of this type of therapy could be maximized by increasing MSC migration, engraftment, survival, and paracrine actions through preconditioning or genetic modification techniques. For having that, more research needs to be directed towards advanced materials as scaffolds and efficient induction factors that will lead to further applications of MSCs in stem cell therapy. Allover, many factors influence the therapeutic potential of MSCs including induction factors, oxygen concentrations, donor age and mechanical stimuli. Therefore, it must be pointed out that optimizing the culture conditions along with choosing the appropriate scaffolds and induction factors is an effective way to improve the therapeutic potential of MSCs to be used as stem cell therapy. Additionally, it's important to conduct properly planned experimental investigations to analyze the risk of fibrosis, maldifferentiation and cancer and to confirm the long-term safety of these treatments. The true clinical efficacy of MSC therapy for renal disorders can only be revealed by the findings of bigger, well-powered, properly designed clinical trials.

Chapter 8

Conclusion

SC therapy has the potential to be a promising new kidney disease treatment. Many animal studies have demonstrated the importance of cell treatment, and because of their allogeneic potential, ability to undergo in vivo renal differentiation, and paracrine mechanisms of action, MSCs have been regarded as a prominent cell type. MSC therapy for renal injury is by far, the most recent options, with promising safety profiles in human trials, despite the relatively crude approach of infusing single cells via intravenous route. MSC have the benefits of being relatively simple to collect and culture, being effectively low-cost and customized treatment options for patients with renal damage. Furthermore, health concerns from MSC treatment have been documented in animal experiments, and the majority of evidence indicates that cells engraftment into damaged organs is temporary. The injection of MSCs has not been associated to any severe side effects in clinical trials. Besides that, to establish the long-term safety of these therapies and to assess the hazards of fibrosis, mal-differentiation, or cancer, carefully designed experimental trials are required. Only larger, well-powered, properly conducted clinical trials will be able to assess the true therapeutic efficacy of MSC treatment in renal illness. A tissue's progenitor cell, in our opinion, is possibly the best source for addressing tissue-specific illnesses. ESCs or iPSCs can be developed to generate this type of cell. The volume of research performed on kidney regeneration employing ESCs and iPSCs is inadequate. To solve the existing limitations regarding these cell types, continued efforts are needed in order to develop step-by-step differentiation methods that lead pluripotent SCs first to generate intermediate mesoderm, then renal progenitors, and finally formation of mature, functional renal cells.

References

Abecassis, M., Bartlett, S. T., Collins, A. J., Davis, C. L., Delmonico, F. L., Friedewald, J. J., Hays, R., Howard, A., Jones, E., Leichtman, A. B., Merion, R. M., Metzger, R. A., Pradel, F., Schweitzer, E. J., Velez, R. L., & Gaston, R. S. (2008). Kidney Transplantation as Primary Therapy for End-Stage Renal Disease: A National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI™) Conference. *Clinical Journal of the American Society of Nephrology*, *3*(2), 471–480. https://doi.org/10.2215/cjn.05021107

Aggarwal, S., Grange, C., Iampietro, C., Camussi, G., & Bussolati, B. (2016). Human CD133+ Renal Progenitor Cells Induce Erythropoietin Production and Limit Fibrosis After Acute Tubular Injury. Scientific Reports, 6(1). https://doi.org/10.1038/srep37270Becherucci, F., Mazzinghi, B., Allinovi, M.,

Angelotti, M. L., & Romagnani, P. (2018). Regenerating the kidney using human pluripotent stem cells and renal progenitors. Expert Opinion on Biological Therapy, 18(7), 795–806. https://doi.org/10.1080/14712598.2018.1492546

Bruce, S. J., Rea, R. W., Steptoe, A. L., Busslinger, M., Bertram, J. F., & Perkins, A. C. (2007). In vitro differentiation of murine embryonic stem cells toward a renal lineage. Differentiation, 75(5), 337–349. https://doi.org/10.1111/j.1432-0436.2006.00149.x

Collino, F., Lopes, J. A., Tapparo, M., Tortelote, G. G., Kasai-Brunswick, T. H., Lopes, G. M., Almeida, D. B., Skovronova, R., Wendt, C. H. C., Miranda, K. R. D., Bussolati, B., Vieyra, A., & Lindoso, R. S. (2020). Extracellular Vesicles Derived from Induced Pluripotent Stem Cells Promote Renoprotection in Acute Kidney Injury Model. Cells, 9(2), 453. https://doi.org/10.3390/cells9020453

Couser, W. G., Remuzzi, G., Mendis, S., & Tonelli, M. (2011). The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney International, 80(12), 1258–1270. https://doi.org/10.1038/ki.2011.368Dai, Y., Chen, W., Huang, J., Yu, X., & Lin, X. (2015). Generation of induced pluripotent stem cells from renal tubular cells of a patient with Alport syndrome. International Journal of Nephrology and Renovascular Disease, 101. https://doi.org/10.2147/ijnrd.s85733

Diep, C. Q., Ma, D., Deo, R. C., Holm, T. M., Naylor, R. W., Arora, N., Wingert, R. A., Bollig, F., Djordjevic, G., Lichman, B., Zhu, H., Ikenaga, T., Ono, F., Englert, C., Cowan, C. A., Hukriede, N. A., Handin, R. I., & Davidson, A. J. (2011). Identification of adult nephron progenitors capable of kidney regeneration in zebrafish. Nature, 470(7332), 95–100. https://doi.org/10.1038/nature09669

Dominici, M., le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D., & Horwitz, E. (2006a). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, 8(4), 315–317. https://doi.org/10.1080/14653240600855905

Dominici, M., le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D., & Horwitz, E. (2006b). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, 8(4), 315–317. https://doi.org/10.1080/14653240600855905

Elger, M., Hentschel, H., Litteral, J., Wellner, M., Kirsch, T., Luft, F. C., & Haller, H. (2003). Nephrogenesis Is Induced by Partial Nephrectomy in the Elasmobranch Leucoraja erinacea. Journal of the American Society of Nephrology, 14(6), 1506–1518. https://doi.org/10.1097/01.asn.0000067645.49562.09

Garcia-Garcia, G., Chapman, J., & Harden, P. (2012). The global role of kidney transplantation. *Indian Journal of Nephrology*, *22*(2), 77. https://doi.org/10.4103/0971-4065.97101

Gupta, S., Verfaillie, C., Chmielewski, D., Kim, Y., & Rosenberg, M. E. (2002). A role for extrarenal cells in the regeneration following acute renal failure. *Kidney International*, *62*(4), 1285–1290. https://doi.org/10.1111/j.1523-1755.2002.kid569.x

Herrera, M., Bussolati, B., Bruno, S., Fonsato, V., Romanazzi, G., & Camussi, G. (2004a). Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. *International Journal of Molecular Medicine*. https://doi.org/10.3892/ijmm.14.6.1035

Herrera, M., Bussolati, B., Bruno, S., Fonsato, V., Romanazzi, G., & Camussi, G. (2004b). Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. *International Journal of Molecular Medicine*. https://doi.org/10.3892/ijmm.14.6.1035

Herrera, M., Bussolati, B., Bruno, S., Morando, L., Mauriello-Romanazzi, G., Sanavio, F., Stamenkovic, I., Biancone, L., & Camussi, G. (2007). Exogenous mesenchymal stem cells localize to the kidney by means of CD44 following acute tubular injury. *Kidney International*, *72*(4), 430–441. https://doi.org/10.1038/sj.ki.5002334

Horwitz, E. M., Gordon, P. L., Koo, W. K. K., Marx, J. C., Neel, M. D., McNall, R. Y., Muul, L., & Hofmann, T. (2002). Isolated allogeneic bone marrow-derived mesenchymal

cells engraft and stimulate growth in children with osteogenesis imperfecta: Implications for cell therapy of bone. *Proceedings of the National Academy of Sciences*, *99*(13), 8932–8937. https://doi.org/10.1073/pnas.132252399

Humphreys, B. D., & Bonventre, J. V. (2008). Mesenchymal Stem Cells in Acute Kidney Injury. *Annual Review of Medicine*, *59*(1), 311–325. https://doi.org/10.1146/annurev.med.59.061506.154239

Humphreys, B. D., Valerius, M. T., Kobayashi, A., Mugford, J. W., Soeung, S., Duffield, J. S., McMahon, A. P., & Bonventre, J. V. (2008). Intrinsic Epithelial Cells Repair the Kidney after Injury. *Cell Stem Cell*, *2*(3), 284–291. https://doi.org/10.1016/j.stem.2008.01.014

Imberti, B., Tomasoni, S., Ciampi, O., Pezzotta, A., Derosas, M., Xinaris, C., Rizzo, P., Papadimou, E., Novelli, R., Benigni, A., Remuzzi, G., & Morigi, M. (2015a). Renal progenitors derived from human iPSCs engraft and restore function in a mouse model of acute kidney injury. *Scientific Reports*, *5*(1). https://doi.org/10.1038/srep08826

Imberti, B., Tomasoni, S., Ciampi, O., Pezzotta, A., Derosas, M., Xinaris, C., Rizzo, P., Papadimou, E., Novelli, R., Benigni, A., Remuzzi, G., & Morigi, M. (2015b). Renal progenitors derived from human iPSCs engraft and restore function in a mouse model of acute kidney injury. *Scientific Reports*, *5*(1). https://doi.org/10.1038/srep08826

Jager, K. J., & Fraser, S. D. (2017). The ascending rank of chronic kidney disease in the global burden of disease study. *Nephrology Dialysis Transplantation*, *32*(suppl_2), ii121–ii128. https://doi.org/10.1093/ndt/gfw330

Jiang, M. H., Li, G., Liu, J., Liu, L., Wu, B., Huang, W., He, W., Deng, C., Wang, D., Li, C., Lahn, B. T., Shi, C., & Xiang, A. P. (2015). Nestin+ kidney resident mesenchymal stem cells for the treatment of acute kidney ischemia injury. *Biomaterials*, *50*, 56–66. https://doi.org/10.1016/j.biomaterials.2015.01.029

Kale, S., Karihaloo, A., Clark, P. R., Kashgarian, M., Krause, D. S., & Cantley, L. G. (2003). Bone marrow stem cells contribute to repair of the ischemically injured renal tubule. *Journal of Clinical Investigation*, *112*(1), 42–49. https://doi.org/10.1172/jci17856

Kim, D., & Dressler, G. R. (2005). Nephrogenic Factors Promote Differentiation of Mouse Embryonic Stem Cells into Renal Epithelia. *Journal of the American Society of Nephrology*, *16*(12), 3527–3534. https://doi.org/10.1681/asn.2005050544

LAJTHA, L. (1979). Stem Cell Concepts. *Differentiation*, *14*(1–3), 23–33. https://doi.org/10.1111/j.1432-0436.1979.tb01007.x

Li, M., & Ikehara, S. (2013). Immunomodulatory Properties and Therapeutic Application of Bone Marrow Derived-Mesenchymal Stem Cells. *Journal of Bone Marrow Research*, *1*(4). https://doi.org/10.4172/2329-8820.1000131

Lin, F., & Igarashi, P. (2003). Searching for Stem/Progenitor Cells in the Adult Mouse Kidney. *Journal of the American Society of Nephrology*, *14*(12), 3290–3292. https://doi.org/10.1097/01.asn.0000098682.51956.06

Lin, S. A., Kolle, G., Grimmond, S. M., Zhou, Q., Doust, E., Little, M. H., Aronow, B., Ricardo, S. D., Pera, M. F., Bertram, J. F., & Laslett, A. L. (2010). Subfractionation of Differentiating Human Embryonic Stem Cell Populations Allows the Isolation of a Mesodermal Population Enriched for Intermediate Mesoderm and Putative Renal Progenitors. *Stem Cells and Development*, *19*(10), 1637–1648. https://doi.org/10.1089/scd.2010.0017

Lindgren, D., Boström, A. K., Nilsson, K., Hansson, J., Sjölund, J., Möller, C., Jirström, K., Nilsson, E., Landberg, G., Axelson, H., & Johansson, M. E. (2011). Isolation and Characterization of Progenitor-Like Cells from Human Renal Proximal Tubules. *The American Journal of Pathology*, *178*(2), 828–837. https://doi.org/10.1016/j.ajpath.2010.10.026

Liu, N., Tian, J., Cheng, J., & Zhang, J. (2013). Migration of CXCR4 gene-modified bone marrow-derived mesenchymal stem cells to the acute injured kidney. *Journal of Cellular Biochemistry*, *114*(12), 2677–2689. https://doi.org/10.1002/jcb.24615

Mae, S. I., Shono, A., Shiota, F., Yasuno, T., Kajiwara, M., Gotoda-Nishimura, N., Arai, S., Sato-Otubo, A., Toyoda, T., Takahashi, K., Nakayama, N., Cowan, C. A., Aoi, T., Ogawa, S., McMahon, A. P., Yamanaka, S., & Osafune, K. (2013a). Monitoring and

robust induction of nephrogenic intermediate mesoderm from human pluripotent stem cells. *Nature Communications*, *4*(1). https://doi.org/10.1038/ncomms2378

Mae, S. I., Shono, A., Shiota, F., Yasuno, T., Kajiwara, M., Gotoda-Nishimura, N., Arai, S., Sato-Otubo, A., Toyoda, T., Takahashi, K., Nakayama, N., Cowan, C. A., Aoi, T., Ogawa, S., McMahon, A. P., Yamanaka, S., & Osafune, K. (2013b). Monitoring and robust induction of nephrogenic intermediate mesoderm from human pluripotent stem cells. *Nature Communications*, *4*(1). https://doi.org/10.1038/ncomms2378

Mae, S. I., Shono, A., Shiota, F., Yasuno, T., Kajiwara, M., Gotoda-Nishimura, N., Arai, S., Sato-Otubo, A., Toyoda, T., Takahashi, K., Nakayama, N., Cowan, C. A., Aoi, T., Ogawa, S., McMahon, A. P., Yamanaka, S., & Osafune, K. (2013c). Monitoring and robust induction of nephrogenic intermediate mesoderm from human pluripotent stem cells. *Nature Communications*, *4*(1). https://doi.org/10.1038/ncomms2378

Mcmahon, A. P. (2005). Patterning of the mammalian kidney. *Kidney International*, *68*(5), 1962. https://doi.org/10.1038/ki.2005.12

Meirelles, L. D. S., Chagastelles, P. C., & Nardi, N. B. (2006). Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *Journal of Cell Science*, *119*(11), 2204–2213. https://doi.org/10.1242/jcs.02932

Morigi, M. (2004). Mesenchymal Stem Cells Are Renotropic, Helping to Repair the Kidney and Improve Function in Acute Renal Failure. *Journal of the American Society of Nephrology*, *15*(7), 1794–1804. https://doi.org/10.1097/01.asn.0000128974.07460.34

Narayanan, K., Schumacher, K. M., Tasnim, F., Kandasamy, K., Schumacher, A., Ni, M., Gao, S., Gopalan, B., Zink, D., & Ying, J. Y. (2013). Human embryonic stem cells differentiate into functional renal proximal tubular–like cells. *Kidney International*, *83*(4), 593–603. https://doi.org/10.1038/ki.2012.442

Nishida, M., Fujimoto, S. I., Toiyama, K., Sato, H., & Hamaoka, K. (2004). Effect of hematopoietic cytokines on renal function in cisplatin-induced ARF in mice. *Biochemical and Biophysical Research Communications*, *324*(1), 341–347. https://doi.org/10.1016/j.bbrc.2004.09.051

Poulsom, R., Forbes, S. J., Hodivala-Dilke, K., Ryan, E., Wyles, S., Navaratnarasah, S., Jeffery, R., Hunt, T., Alison, M., Cook, T., Pusey, C., & Wright, N. A. (2001). Bone marrow contributes to renal parenchymal turnover and regeneration. *The Journal of Pathology*, *195*(2), 229–235. https://doi.org/10.1002/path.976

Prockop, D. J. (1997). Marrow Stromal Cells as Stem Cells for Nonhematopoietic Tissues. *Science*, *276*(5309), 71–74. https://doi.org/10.1126/science.276.5309.71

Sagrinati, C., Netti, G. S., Mazzinghi, B., Lazzeri, E., Liotta, F., Frosali, F., Ronconi, E., Meini, C., Gacci, M., Squecco, R., Carini, M., Gesualdo, L., Francini, F., Maggi, E., Annunziato, F., Lasagni, L., Serio, M., Romagnani, S., & Romagnani, P. (2006). Isolation and Characterization of Multipotent Progenitor Cells from the Bowman's Capsule of Adult Human Kidneys. *Journal of the American Society of Nephrology*, *17*(9), 2443–2456. https://doi.org/10.1681/asn.2006010089

Steenhard, B. M., Isom, K. S., Cazcarro, P., Dunmore, J. H., Godwin, A. R., St. John, P. L., & Abrahamson, D. R. (2005). Integration of Embryonic Stem Cells in Metanephric Kidney Organ Culture. *Journal of the American Society of Nephrology*, *16*(6), 1623–1631. https://doi.org/10.1681/asn.2004070584

Stokman, G., Leemans, J. C., Claessen, N., Weening, J. J., & Florquin, S. (2005). Hematopoietic Stem Cell Mobilization Therapy Accelerates Recovery of Renal Function Independent of Stem Cell Contribution. *Journal of the American Society of Nephrology*, *16*(6), 1684–1692. https://doi.org/10.1681/asn.2004080678

Takahashi, K., & Yamanaka, S. (2006). Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, *126*(4), 663–676. https://doi.org/10.1016/j.cell.2006.07.024

Takasato, M., Er, P. X., Becroft, M., Vanslambrouck, J. M., Stanley, E. G., Elefanty, A. G., & Little, M. H. (2013). Directing human embryonic stem cell differentiation towards a renal lineage generates a self-organizing kidney. *Nature Cell Biology*, *16*(1), 118–126. https://doi.org/10.1038/ncb2894

Takasato, M., Takasato, M., X. Er, P., S. Chiu, H., & H. Little, M. (2015). Generation of kidney organoids from human pluripotent stem cells. *Protocol Exchange*. https://doi.org/10.1038/protex.2015.087

Vigneau, C., Polgar, K., Striker, G., Elliott, J., Hyink, D., Weber, O., Fehling, H. J., Keller, G., Burrow, C., & Wilson, P. (2007a). Mouse Embryonic Stem Cell–Derived Embryoid Bodies Generate Progenitors That Integrate Long Term into Renal Proximal TubulesIn Vivo. *Journal of the American Society of Nephrology*, *18*(6), 1709–1720. https://doi.org/10.1681/asn.2006101078

Vigneau, C., Polgar, K., Striker, G., Elliott, J., Hyink, D., Weber, O., Fehling, H. J., Keller, G., Burrow, C., & Wilson, P. (2007b). Mouse Embryonic Stem Cell–Derived Embryoid Bodies Generate Progenitors That Integrate Long Term into Renal Proximal TubulesIn Vivo. *Journal of the American Society of Nephrology*, *18*(6), 1709–1720. https://doi.org/10.1681/asn.2006101078

Wagers, A. J., & Weissman, I. L. (2004). Plasticity of Adult Stem Cells. *Cell*, *116*(5), 639–648. https://doi.org/10.1016/s0092-8674(04)00208-9

Walsh, D. W., Roxburgh, S. A., McGettigan, P., Berthier, C. C., Higgins, D. G., Kretzler, M., Cohen, C. D., Mezzano, S., Brazil, D. P., & Martin, F. (2008). Co-regulation of Gremlin and Notch signalling in diabetic nephropathy. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1782*(1), 10–21. https://doi.org/10.1016/j.bbadis.2007.09.005

Weimar, I., Voermans, C., Bourhis, J. H., Miranda, N., van den Berk, P., Nakamura, T., de Gast, G., & Gerritsen, W. (1998). Hepatocyte growth factor/scatter factor (HGF/SF) affects proliferation and migration of myeloid leukemic cells. *Leukemia*, *12*(8), 1195–1203. https://doi.org/10.1038/sj.leu.2401080

Wolfe, R. A., Ashby, V. B., Milford, E. L., Ojo, A. O., Ettenger, R. E., Agodoa, L. Y., Held, P. J., & Port, F. K. (1999). Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. *New England Journal of Medicine*, *341*(23), 1725–1730. https://doi.org/10.1056/nejm199912023412303

Yamamoto, M., Cui, L., Johkura, K., Asanuma, K., Okouchi, Y., Ogiwara, N., & Sasaki, K. (2006). Branching ducts similar to mesonephric ducts or ureteric buds in teratomas originating from mouse embryonic stem cells. *American Journal of Physiology-Renal Physiology*, *290*(1), F52–F60. https://doi.org/10.1152/ajprenal.00001.2004

Yokoo, T., Fukui, A., Ohashi, T., Miyazaki, Y., Utsunomiya, Y., Kawamura, T., Hosoya, T., Okabe, M., & Kobayashi, E. (2006). Xenobiotic Kidney Organogenesis from Human Mesenchymal Stem Cells Using a Growing Rodent Embryo. *Journal of the American Society of Nephrology*, *17*(4), 1026–1034. https://doi.org/10.1681/asn.2005101043

Zhou, T., Benda, C., Duzinger, S., Huang, Y., Li, X., Li, Y., Guo, X., Cao, G., Chen, S., Hao, L., Chan, Y. C., Ng, K. M., Cy Ho, J., Wieser, M., Wu, J., Redl, H., Tse, H. F., Grillari, J., Grillari-Voglauer, R., . . . Esteban, M. A. (2011). Generation of Induced Pluripotent Stem Cells from Urine. *Journal of the American Society of Nephrology*, *22*(7), 1221–1228. https://doi.org/10.1681/asn.2011010106

Lajtha, L. G., & Oliver, R. (1962). Cell Population Kinetics following Different Regimes of Irradiation. *The British Journal of Radiology*, *35*(410), 131–140. https://doi.org/10.1259/0007-1285-35-410-131

Scadden, D., & Srivastava, A. (2012). Advancing Stem Cell Biology toward Stem Cell Therapeutics. *Cell Stem Cell*, *10*(2), 149–150. https://doi.org/10.1016/j.stem.2012.01.010

Mias, C., Trouche, E., Seguelas, M. H., Calcagno, F., Dignat-George, F., Sabatier, F., Piercecchi-Marti, M. D., Daniel, L., Bianchi, P., Calise, D., Bourin, P., Parini, A., & Cussac, D. (2008). Ex Vivo Pretreatment with Melatonin Improves Survival, Proangiogenic/Mitogenic Activity, and Efficiency of Mesenchymal Stem Cells Injected into Ischemic Kidney. *Stem Cells*, *26*(7), 1749–1757. https://doi.org/10.1634/stemcells.2007-1000

Tögel, F. E., & Westenfelder, C. (2010). Mesenchymal stem cells: a new therapeutic tool for AKI. *Nature Reviews Nephrology*, *6*(3), 179–183. https://doi.org/10.1038/nrneph.2009.229

Tögel, F. E., & Westenfelder, C. (2012). Kidney Protection and Regeneration Following Acute Injury: Progress Through Stem Cell Therapy. *American Journal of Kidney Diseases*, *60*(6), 1012–1022. https://doi.org/10.1053/j.ajkd.2012.08.034

Mias, C., Trouche, E., Seguelas, M. H., Calcagno, F., Dignat-George, F., Sabatier, F., Piercecchi-Marti, M. D., Daniel, L., Bianchi, P., Calise, D., Bourin, P., Parini, A., & Cussac, D. (2008b). Ex Vivo Pretreatment with Melatonin Improves Survival, Proangiogenic/Mitogenic Activity, and Efficiency of Mesenchymal Stem Cells

Injected into Ischemic Kidney. *Stem Cells*, *26*(7), 1749–1757. https://doi.org/10.1634/stemcells.2007-1000

Romagnani, P., & Remuzzi, G. (2014). CD133+ renal stem cells always co-express CD24 in adult human kidney tissue. *Stem Cell Research*, *12*(3), 828–829. https://doi.org/10.1016/j.scr.2013.12.011