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# Exploring Nephron Repair via Embryonic Stem Cells: A Review of Stem Cell-Based Kidney Therapies

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**ABSTRACT**

The nephron, the functional unit of the kidney, is responsible for filtration, reabsorption, and secretion, critical processes for maintaining systemic homeostasis. Damage to nephrons due to pathological conditions such as diabetic nephropathy, glomerulonephritis, and ischemic acute kidney injury can lead to irreversible renal dysfunction and progression to end-stage renal disease. Although current therapeutic options such as dialysis and kidney transplantation have alleviated the symptoms of renal failure, there is no curative treatment to restore native nephron function. Recent advances in regenerative medicine, particularly through the use of embryonic stem cells (ESCs), have shown promising potential in nephron repair. ESCs, due to their pluripotency, possess the ability to differentiate into various renal cell types, including podocytes, proximal tubular cells, and renal endothelial cells, all of which are vital components for nephron regeneration. Studies have demonstrated that renal progenitor cells derived from embryonic stem cells are capable of integrating into injured nephron structures, facilitating tissue repair, and contributing to the partial recovery of renal function in various experimental models. Nevertheless, significant obstacles remain, including immune compatibility, the refinement of differentiation techniques, and the assurance of long-term stability and functionality of regenerated nephron units. This review critically examines recent progress in ESC-mediated nephron regeneration, focusing on the molecular mechanisms that regulate nephron lineage commitment, advancements achieved in both experimental and translational studies, and the emerging therapeutic prospects for chronic kidney disease. The continued exploration of ESC-based therapies for nephron regeneration holds transformative potential for the future of nephrology, offering a novel approach to restoring renal function in patients with nephron loss.

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**KEYWORDS:**

Embryonic Stem Cells, Nephrons, Kidney Diseases, Regenerative Medicine, Cell Differentiation

## INTRODUCTION

The nephron, a critical functional unit of the kidney, plays a crucial role in maintaining overall bodily homeostasis. It regulates fluid levels, electrolyte balance, acid-base equilibrium, and waste elimination through processes like filtration and reabsorption. The nephron is composed of multiple segments, such as the glomerulus, proximal and distal convoluted tubules, the loop of Henle, and collecting ducts, all of which collectively support the kidney's essential functions. These functions include blood filtration, blood pressure regulation, and metabolic equilibrium (Gantsova et al., 2024). However, when the nephrons are damaged, the kidney's ability to perform these tasks is compromised, leading to a range of systemic complications. Conditions like diabetic nephropathy, glomerulonephritis, hypertensive nephropathy, and acute kidney injury (AKI) often result in nephron loss, which is a significant factor in the progression of chronic renal failure. These diseases cause irreversible damage to nephron structures, and if left untreated, can lead to end-stage renal disease (ESRD) (Gusev et al., 2021). The gradual loss of nephron function is reflected in a decrease in glomerular filtration rate (GFR), which may eventually require interventions such as dialysis or a kidney transplant. Despite these interventions, they are not curative and present their own set of challenges, including high costs, risk of infections, and complications related to organ

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rejection in transplantation. In recent years, regenerative medicine has become a candidate treatment modality for overcoming the constraints of current kidney therapies. Because of their pluripotency, Embryonic Stem Cells (ESCs) are an ideal candidate for nephron regeneration. ESCs can differentiate into almost any cell type and it has been suggested that ESC-derived renal progenitor cells may be used to regenerate, replace, or repair injured nephron structures. Therapies with ESCs offer the potential to regenerate functional nephrons and achieve restoration of kidney function, as differentiated cells of the renal lineage like podocytes, proximal tubular and endothelial cells are responsible for maintaining the architecture and physiology of a nephron (Liu et al., 2020).

Moreover, advances in ESC differentiation protocols and tissue engineering have allowed for the development of strategies that may enable the integration of ESC-derived nephron cells into damaged renal tissue, promoting tissue repair and functional recovery. However, despite the encouraging preclinical results, the translation of ESC-based therapies into clinical practice faces several challenges, including immune rejection, ethical concerns, and the optimization of cell differentiation protocols.Therefore, the purpose of this review is to provide a comprehensive evaluation of current progress in ESC-based nephron regeneration, elucidate the underlying molecular mechanisms of nephron lineage differentiation, and discuss the translational potential and future directions of this emerging therapeutic approach in renal medicine. (Liu et al., 2020).

**Anatomy and Function of the Nephron**

The basic unit of kidney action is the nephron, which is a component in the normalization of the body internal environment. It makes it easier to filter blood, remove waste products, and preserve the functioning of the vital processes, including electrolytes, fluid balance, and acid-base balance. Every kidney contains about one million nephrons and every nephron consists of two main components: the renal corpuscle and the renal tubule. All these parts act in harmony to make sure that there is appropriate filtration, selective reabsorption and secretion, which is vital in ensuring homeostasis (Schwartz & Rashid, 2021).

The initial structure that is involved in the process of blood filtration is the renal corpuscle which is made up of the glomerulus and Bowman's capsule. The glomerulus comprises a tangle of capillaries by which the blood enters through the afferent arteriole. Blood is filtered in the glomerulus as it flows into the glomerulus, the small molecules like water, glucose and waste products are filtered and eliminated in Bowman's capsule which is a cup shaped structure that wraps around the glomerulus. The filtration barrier consists of fenestrated endothelial cells, the basement membrane, and podocytes and only certain substances such as water, ions, and small molecules can pass through it and larger substances such as proteins and blood cells are retained in the bloodstream (Hoenig & Hladik, 2018).

Once the filtrate enters Bowman's capsule, it travels into the proximal convoluted tubule (PCT), the first part of the renal tubule. The PCT is responsible for reabsorbing a significant portion of the filtered substances back into the bloodstream. Around 65-70% of water, sodium, chloride, glucose, amino acids, and bicarbonate are reabsorbed in this section, using both passive diffusion and active transport. The PCT's walls are lined with microvilli, which increase surface area to maximize reabsorption efficiency. In addition to reabsorption, the PCT also secretes waste products like hydrogen ions and certain drugs into the filtrate, contributing to acid-base balance and detoxification (Koeppen & Stanton, 2018).

The U shaped structure that follows the PCT is the loop of Henle which is vital in development of concentration gradients in the renal medulla that is vital to the capacity of the kidney to concentrate urine and retain water. The lower limb of the loop is permeable to water but impermeable to solutes resulting in reabsorption of water into the tissue surrounding it, raising the osmolarity of the filtrate. The ascending limb on the other hand actively pushes sodium, potassium and chloride ions out of the filtrate and is impermeable to water, thereby diluting the filtrate. It is a process that creates a hyperosmolar environment in the medulla which helps in the reabsorption of water in the nephron later. The loop of Henle is a countercurrent multiplier system that is necessary in the ability of the kidney to concentrate urine and fluid balance (Hosseinzadeh, 2025).

The distal convoluted tubule (DCT) is the vapor that fine-tunes the electrolyte and fluid balance by specifically reabsorbing sodium, calcium and chloride ions, which are regulated by hormones including the aldosterone and parathyroid hormone. It is also important in the maintenance of acid base balance whereby it reabsorbs bicarbonate and releases hydrogen ions to the filtrate. Moreover, DCT participates in the release of potassium ions and waste products, which is why the nephron completes its task of maintaining the fluid and electrolytes and waste removal. This fine balance is what makes the environment in the body not to be affected by the external conditions (Valinsky, 2017).

**Pathophysiology of Nephron Damage**

The key features of numerous renal pathologies and the leading causes of renal dysfunction are nephron damage. Damage of the nephron causes kidney failure, which causes poor filtration, electrolyte imbalance and build-up of waste products. Understanding the pathophysiological processes

underlying nephron damage is crucial for developing therapeutic options that facilitate renal regeneration and improve patient outcomes in renal diseases (Romagnani et al., 2017).

One of the most common causes of end-stage renal disease (ESRD) and chronic kidney disease (CKD) is diabetic nephropathy. Advanced glycation end-products (AGEs) accumulated as a result of chronic hyperglycemia in diabetes cause inflammation, fibrosis, and glomerular injury. The changes cause thickening of the glomerular basement membrane, mesangio-expansion and podocyte damage that cause proteinuria and progressive nephron loss. Continuous destruction of nephrons in diabetic nephropathy hastens loss of renal functions and also leads to kidney failure (Krolewski et al., 2017).

CKD is defined as progressive damage of kidney functions, i.e., loss of glomerular filtration rate (GFR) and / or markers of kidney damage (e.g., albuminuria) over a period of more than 3 months. The reasons behind CKD are diverse and they encompass high blood pressure, nephritis of the glomeruli, polycystic kidney disease, and obstructive nephropathy. In the long run, CKD causes nephron loss, interstitial fibrosis and vascular damage that further worsens the deterioration of kidney function. The end result of the progressive CKD is a loss of kidney activity and the necessity of dialysis or transplantation (Romagnani et al., 2017).

Also referred to as acute renal failure, Acute Kidney Injury (AKI) is a condition of sudden loss in kidney functions in a period of hours to days. It may be prerenal, intrinsic and postrenal. Intrinsic causes of AKI are often ischemia (because of hypoperfusion), nephrotoxic injury (nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotics, or contrast agents), and acute glomerulonephritis. The nephron damage in AKI frequently includes tubular necrosis, thereby disrupting reabsorption and secretion, causing electrolyte disequilibrium, fluid retention, and accumulation of waste (Kellum et al., 2021).

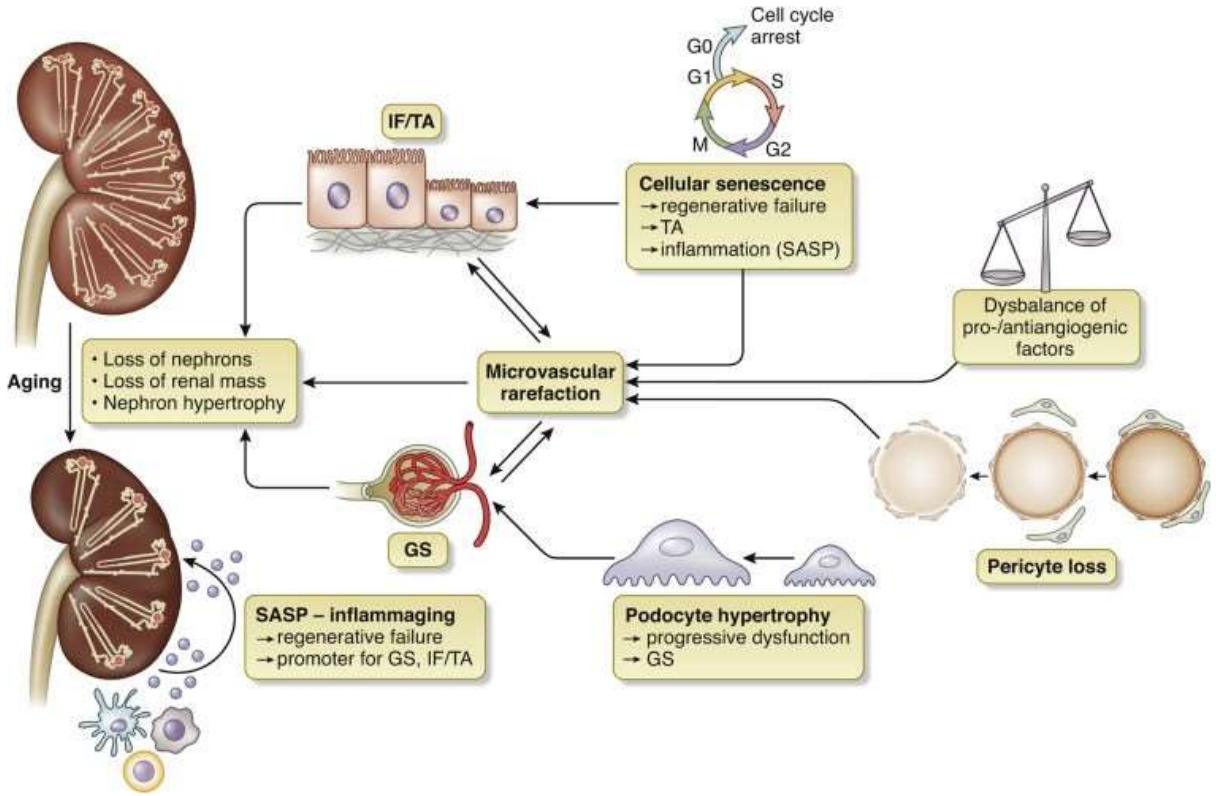


**Figure 01: The aging kidney loses nephrons (Schmitt & Melk, 2017)**

Figure 01 illustrates the complex mechanisms underlying age-related renal degeneration and the interplay between cellular senescence, inflammation, and vascular injury. Aging induces a gradual loss of nephrons and renal mass, leading to compensatory nephron hypertrophy. Over time, senescent renal cells undergo a state of permanent cell-cycle arrest and secrete a variety of inflammatory mediators collectively known as the senescence-associated secretory phenotype (SASP). These factors drive a state of chronic low-grade inflammation, also referred to as "inflammaging," which promotes glomerulosclerosis (GS) and interstitial fibrosis with tubular atrophy (IF/TA)—two major histopathological features of chronic kidney disease. Concurrently, microvascular rarefaction, or the progressive loss of renal capillaries, exacerbates tissue hypoxia and accelerates fibrotic remodeling. The decline in pericyte function and the imbalance between pro- and anti-angiogenic signals further compromise vascular integrity, reducing oxygen delivery to renal parenchyma. Podocyte hypertrophy, a compensatory response to nephron loss,

eventually results in structural stress and glomerular dysfunction. Collectively, these interconnected processes culminate in regenerative failure, persistent inflammation, and progressive decline in renal function observed with aging.

Hypertension is an important risk that can cause kidney damage and development of CKD. Chronic hypertension results in enhanced mechanical strain on the glomeruli resulting in endothelial dysfunction, glomerulosclerosis and tubulointerstitial fibrosis. This leads to the destruction of nephrons in the long run. Moreover, hypertensive nephropathy usually worsens the existing conditions like diabetes and atherosclerosis and increases the rate of kidney disease. The damage to nephrons leads to the loss of nephron function leading to the impaired kidney functioning and clinical manifestation of renal disease. The filtration and homeostasis functions of the kidneys are impaired and result in a number of prominent characteristics of renal failure:

Reduced Glomerular Filtration Rate (GFR), As nephron damage advances, GFR reduces, which is the major measure of kidney activity. The reduction in GFR causes the build-up of waste products, including urea, creatinine, and uric acid, in the blood, which may cause uremia and related symptoms, including nausea, fatigue, and confusion. The leakage of proteins, especially albumin, into the urine is caused by damages to the glomerular filtration barrier, especially the podocytes. One of the key symptoms of kidney disease progression is proteinuria, which is usually an early sign of glomerular injury. Continuous proteinuria is linked to a poor prognosis in CKD and diabetic nephropathy. The damage on the nephrons interferes with the kidney and makes them unable to regulate electrolytes, which results in imbalances. In the example of AKI and CKD, hyperkalemia (elevated potassium) and hyponatremia (low sodium) are typical because of the lack of tubular functionality. There can also be disruptions in the calcium and phosphate metabolism, especially in CKD, that results in secondary hyperparathyroidism and bone mineral disease. The kidney is very important in maintaining the blood pH level by releasing hydrogen ion and reabsorbing bicarbonate. This is affected by nephron damage resulting in metabolic acidosis, especially when CKD or AKI advanced. Damaged nephrons are not able to effectively excrete excess fluid which causes fluid retention and edema. This may lead to swelling of the extremities, congestion of the lungs (in severe cases) and high blood pressure (Schmitt & Melk, 2017).

**Embryonic Stem Cells (ESCs) & Pluripotency of ESCs:**

Embryonic stem cells (ESCs) are pluripotent cells that are formed as the inner cell mass of the blastocyst during early embryonic development. The distinctive property of these cells is that they can be self-renewed and transformed into any body cell type and hence make them a potent regenerative medicine tool. Their pluripotency and developmental plasticity can distinguish them compared to other classes of stem cells, which are more limited in their differentiation potential, e.g. adult stem cells. The fact that ESCs can produce a broad spectrum of cell types has generated significant interest in their potential role in treating several degenerative diseases, such as kidney diseases, by providing a source of cells that can regenerate damaged tissues. Under certain conditions, ESCs can be grown and cloned in vitro without losing its pluripotent state and induced to develop into specialized cell types to treat diseases. The identifying characteristic of ESCs is pluripotency, i.e., the ability to develop into all three primary germ layers, i.e., ectoderm, mesoderm, and endoderm. This capability enables them to produce any form of cell in the body virtually and some of these cells include those in the heart, liver, lungs, and kidneys. Ectoderm, Differentiation This tissue forms skin, neurons, and sensory organs. Mesoderm, Precursor of muscle, bone, blood cells and kidney cells. Endoderm, Forms inner organs, like the pancreas, liver, and gastrointestinal tract (Kim et al., 2015).

ESCs have demonstrated potential in nephron regeneration as they have the capacity to differentiate into renal progenitor cells, capable of differentiating into the various components of the nephron, including podocytes, tubular cells and renal endothelial cells. This differentiation ability to form cell types that are kidney specific is an important feature of their promise in kidney disease treatment, in which nephron loss or dysfunction is the main pathology (Bussolati & Camussi, 2015).

Directing ESCs to develop into particular renal cell types, including podocytes, proximal tubular cells, and endothelial cells is a major process in kidney regenerative therapy. This differentiation process is associated with different signaling pathways and transcription factors. As an example: Wnt/b-catenin signaling, Plays a crucial role in the differentiation of ESCs into renal progenitor cells, and their further differentiation into nephron structures. Notch signaling, Controls cell fate choice in nephron differentiation, determined the development of particular renal cells. BMP (Bone Morphogenetic Protein) signaling, Relevant to the induction of nephron progenitors of ESCs (Nishinakamura et al., 2017).

In vitro differentiation studies have been undertaken to recapitulate the developmental signals of nephrogenesis to enable ESCs to differentiate into functional renal progenitors, which can be further used to transplant or regenerate tissue. Nevertheless, there are still certain obstacles in attaining effective differentiation and sustaining the functionality of the derived renal cells along with the appropriate combination into harmed kidney tissue (Mari & Winyard, 2015).

Regenerative medicine using ESCs has the potential to revolutionize the treatment of chronic kidney diseases (CKD) and acute kidney injury (AKI). ESC-based therapies could restore damaged nephron components, regenerate functional nephrons, and ultimately improve kidney function. Potential applications of ESCs in nephrology include: Nephron Regeneration, ESCs can potentially regenerate damaged nephrons by differentiating into renal progenitor cells, which can then repair or replace dysfunctional nephrons. Cell-based Therapies, Transplantation of ESC-derived nephron cells, such as podocytes or proximal tubular cells, into damaged kidneys could restore renal function, particularly in conditions such as diabetic nephropathy, glomerulonephritis, and AKI. Kidney Disease Models, ESCs can be used to create in vitro or in vivo models of kidney disease for drug testing and research, facilitating the development of new therapies. The ability to derive large quantities of renal cells from ESCs also holds promise for generating autologous tissues or for treating patients with renal failure who do not have access to suitable kidney donors for transplantation (Tamargo et al., 2024).

**Mechanisms of Nephron Differentiation from ESCs**

Embryonic stem cell (ESC) differentiation into nephron components is a highly coordinated process that is stimulated by particular molecular signaling pathways and transcriptional factors. These signaling pathways control the development of ESCs, which become renal progenitors that can develop into podocytes, proximal tubular cells, endothelial cells, and other essential nephron parts. The knowledge of these differentiation mechanisms will be important in the development of effective nephron regeneration strategies and treatment of kidney diseases.

Nephron differentiation of ESCs follows a close developmental trajectory to that followed during kidney development in the embryo. ESCs differentiate into renal progenitor cells, and various signaling pathways play a central role in the process of cell fate regulation and morphogenesis (Takasato et al., 2014). These pathways include:

The Wnt signaling is a crucial pathway in the development of kidneys, especially in the differentiation of nephrons. In the initial phases of ESC differentiation, the renal progenitors are induced by the Wnt/b-catenin signal. Wnt ligands stimulate the activation of the b-catenin pathway resulting in the expression of transcription factors specific to kidneys such as Pax2 and Six2 that are necessary in the specification of the nephron progenitor cells. The stimulation of Wnt signaling induces the differentiation of intermediate mesoderm, the predecessor of nephron cells (Wang et al., 2018).

Notch signaling controls cell fate choices during nephron formation, particularly during podocyte and tubular cell formation. Notch signaling is known to sustain the progenitor pool and at the same time induce differentiation into lineages of particular nephrons. Notch signaling can be used to stimulate the development of podocytes and mesangial cells, which are important glomerular constituents, in ESC differentiation protocols. The differentiation of ESCs to renal progenitor requires FGF signaling (Mukherjee et al., 2019).

The FGF2, FGF7 and other FGF family members play a role in early nephrogenesis, which stimulates the creation of metanephric mesenchyme, the precursor of nephron cells. The FGF signaling assists in maintaining nephron progenitor self-renewal and formation of renal epithelial cells (Trueb et al., 2013).

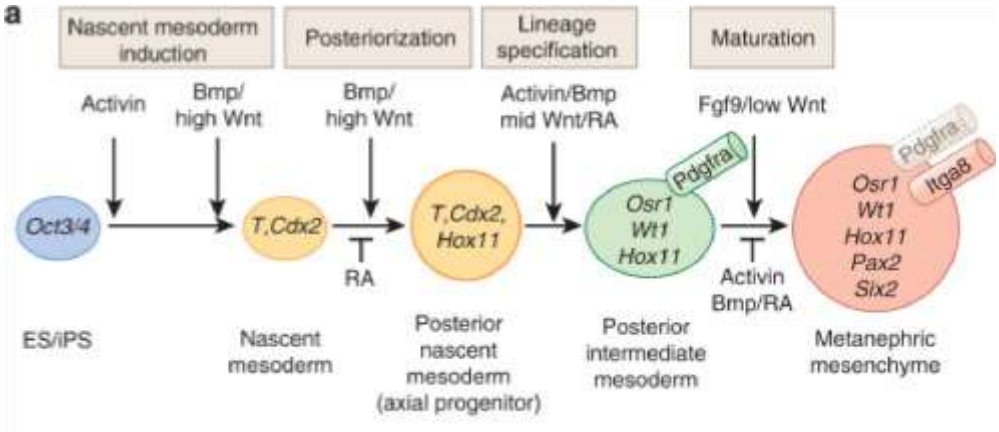


**Figure 02: Novel model of directed differentiation of pluripotent stem cells toward the metanephric mesenchyme (Taguchi & Nishinakamura, 2015)**

BMP signaling, particularly BMP7, is critical for the induction of nephron progenitors during ESC differentiation. BMP signaling helps establish the anterior-posterior axis of the developing kidney and promotes the differentiation of ESCs into specific nephron cell types. BMP7 has been shown to induce the formation of renal

tubules and promote nephron formation from ESCs in culture (Sallam, 2021).

TGF-β signaling is crucial for the epithelial-to-mesenchymal transition (EMT), a process that is essential for the formation of nephron cells, particularly in the development of the renal tubular epithelium. TGF-β can also influence fibrosis in damaged kidneys, and manipulating this pathway in ESC differentiation protocols may help enhance renal cell differentiation while limiting excessive fibrotic responses (Xu et al., 2009).

ESC nephron differentiation procedure is generally a progression of distinct phases which are comparable to the embryonic kidney development. These stages include:

Stage 1: Nephron Progenitor Specification and Mesoderm Formation, The first phase in nephron differentiation is the specification of mesodermal progenitors of ESCs. Signaling pathways including Wnt/b-catenin and FGF induce this. The mesodermal progenitors then develop nephron progenitor cells characterized by the expression of transcription factors such as Pax2 and Six2. Such progenitors will become nephron components (Davidson et al., 2019).

Stage 2: Nephron Progenitor Induction, The nephron progenitors are further differentiated to become committed to particular nephron lineages. The WT1 and Lmx1b expression is the indicator of the formation of podocytes, and Cux1 is connected with the formation of tubular epithelial cells. BMP and FGF signaling also play an important role during this phase in facilitating differentiation of renal progenitors to mature nephron cells (Nishinakamura et al., 2017).

Stage 3: Nephron Maturation, At this stage, the nephron progenitor cells become specialized into the types of nephron cells, such as podocytes, proximal tubule cells and renal endothelial cells. The development of the glomerulus and the setting of the renal tubules are some of the most important occurrences in the maturation of the nephron. At this stage, the cells start to take their ultimate structural and functional forms in the process of filtration, reabsorption, as well as secretion (Perl et al., 2022).

Stage 4: Functional Integration, The last differentiation stage is functional integration where the differentiated cells of the nephron are incorporated into functional renal structures. The cells have to form appropriate cell-cell junctions, create filtration barriers (in podocytes) and start performing their physiological roles, including ionic transport, waste filtration, and fluid homeostasis at this stage (Lv et al., 2025).

The process of differentiation of ESCs into nephron progenitors and nephron cells is a complex one and is regulated by a system of molecular signaling pathways and transcription factors. A clear comprehension of these processes is essential in the creation of effective stem cell-based therapeutic interventions on the nephron regeneration in kidney diseases. Although considerable improvements have been made in the optimization of ESC differentiation protocols, there are still difficulties to attain efficient differentiation, the functionality of the obtained renal cells and the integration of these cells into damaged kidney tissue. Future studies on such molecular pathways will be the basis of future therapeutic interventions to restore kidney functions in patients who have lost their nephrons (Nishinakamura et al., 2017).

Furthermore, advances in ESC-centered preclinical and emerging clinical studies have expanded the understanding of nephron regeneration. These studies demonstrate that ESC-derived renal progenitor cells can reconstruct nephron structures, enhance tissue repair, and improve renal function in experimental models of kidney injury. Collectively, these findings highlight the translational potential of ESC-based nephron repair as a promising strategy to reverse renal damage and restore kidney function in chronic kidney disease.

## CONCLUSION

The potential for embryonic stem cells (ESCs) to regenerate damaged nephrons and restore kidney function represents a groundbreaking advancement in regenerative medicine. Through their pluripotency and ability to differentiate into various nephron components, ESCs offer a promising solution for addressing kidney diseases that result in nephron loss, such as diabetic nephropathy, acute kidney injury (AKI), and chronic kidney disease (CKD). The intricate molecular signaling pathways, including Wnt/β-catenin, Notch, BMP, and FGF, govern the differentiation of ESCs into renal progenitor cells and specialized nephron cell types, including podocytes, proximal tubular cells, and endothelial cells. Understanding fyuui0[]these pathways has allowed for the development of differentiation protocols that closely mimic embryonic kidney development. Despite significant progress in the field, several challenges remain in translating ESC-based therapies into clinical practice. Key hurdles include optimizing differentiation protocols, ensuring the functionality and survival of differentiated cells post-transplantation, addressing immune rejection, and minimizing tumorigenicity risks. Furthermore, scalability, cost-effectiveness, and long-term safety remain major concerns in clinical implementation. While ESC-based regenerative therapies hold immense potential, they are still in the experimental phase, requiring further research and rigorous testing to establish their safety and efficacy in human patients. With continued advancements in stem cell biology, gene editing, and immunomodulation, ESC-based nephron regeneration may soon become a viable therapeutic option for patients with kidney failure, offering a promising alternative to dialysis and organ transplantation.

**Ethical Consideration:**

Ethical clearance was not required for this study.

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