

Angiogenesis and Vascular Repair in Acute Kidney Injury

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ABSTRACT

Chronic kidney disease (CKD) is one of the most dangerous medical illnesses that can be caused by acute kidney injury (AKI), which is characterised by the sudden cessation of normal kidney function. This condition can also lead to other major complications. Abnormalities of the endothelium, inflammation, and oxidative stress are all factors that contribute to the development of acute kidney injury (AKI), which primarily impacts the vasculature of the kidneys. Renal regeneration is dependent on angiogenesis and vascular repair pathways, which include hypoxia-inducible pathways, vascular endothelial growth factor signalling, and the activation of endothelial progenitor cells. These pathways are essential for the regeneration of the human kidney. Angiogenesis that is not properly regulated can, unfortunately, hasten the onset of chronic kidney disease (CKD), which can then result in maladaptive repair and fibrosis. In acute kidney injury (AKI), there is an immediate need for novel therapeutic approaches that focus on the molecular mechanisms of vascular repair in order to enhance regeneration while simultaneously reducing pathological remodelling. The purpose of this study is to discuss the function of angiogenesis and vascular repair in acute kidney injury (AKI), as well as to highlight potential treatment methods that could improve renal outcomes.

Keywords- Acute kidney injury, angiogenesis, vascular repair, endothelial dysfunction, vascular endothelial growth factor.

I. INTRODUCTION

Acute kidney injury (AKI) is a frequent medical disorder that can manifest itself in a number of different ways. These include an increased risk of death, longer hospital stays, and the possibility of developing chronic kidney disease (CKD)[1]. The incidence of acute kidney injury (AKI) varies depending on the type of care setting and the definition of the condition[2]. The incidence of acute kidney injury (AKI) ranges from ten to fifteen percent among hospitalized patients, with intensive care units having a frequency of fifty percent or more. It is referred to as community-acquired acute kidney injury (AKI), and it is said to be extremely common[3]. This type of AKI occurs when it occurs outside of a healthcare center. Wonnacott et al. conducted a study in which they evaluated the epidemiology, risk factors, and outcomes of patients who had CA-AKI (n = 686), as well as hospital-acquired AKI (n = 334)[4-7]. They demonstrated that the hospital admission rate for CA-

AKI was approximately twice as high as the admission rate for HA-AKI, which was 2.1%, for persons who had risk factors that were comparable to those of CA-AKI[8]. Despite having a more severe form of acute kidney injury (AKI), they also found that individuals with CA-AKI have superior survival rates and comparable renal outcomes because of their condition[9]. An increasing number of factors, such as an aging population, an increase in the number of comorbidities that put patients at risk, an increase in the number of nephrotoxic drugs used, and an increase in the number of invasive operations, may be responsible for the rise in the prevalence of acute kidney injury (AKI)[10-13].

II. CAUSE

According to the conventional wisdom, acute kidney injury (AKI) can originate from three distinct sources: pre-renal, renal, and post-renal[14]. When it

comes to each of these groups, there are a lot of different beginnings. An increase in the amount of blood that flows to the kidneys is referred to as pre-renal. It is possible that this is the result of systemic hypoperfusion brought on by low blood volume or blood pressure[15]. Alternatively, it may be the outcome of renal artery stenosis or aortic dissection, both of which lead to selective hypoperfusion to the kidneys. There are many different causes that can lead to acute tubular necrosis, which is a disorder that affects the kidneys.

In the majority of cases, conditions such as chronic renal ischemia, sepsis, and nephrotoxins are present. Pre-renal injury can develop into renal injury if the offending element is exposed to over a prolonged period of time that is sufficient to cause cellular damage[16]. This is something that should be taken into consideration. The majority of complications that occur after renal surgery are obstructive in nature, which means that they cause obstructions in the filtration system and, in the long term, the failure of the kidneys **Fig.1.**

The most common causes of urethral obstructions are stones in the urinary tract, tumors, and other urethral blockages. Another noteworthy point to bear in mind is that acute kidney injury (AKI) may not always be the result of a unilateral blockage, particularly if the blockage is gradual like a tumor[17]. This is due to the fact that the healthy kidney on the opposite side of the body can sometimes compensate for the operation of the kidney that is damaged. Because of this, the most common reason for acute kidney injury (AKI) following renal transplantation is an obstruction of the bladder outflow[18].

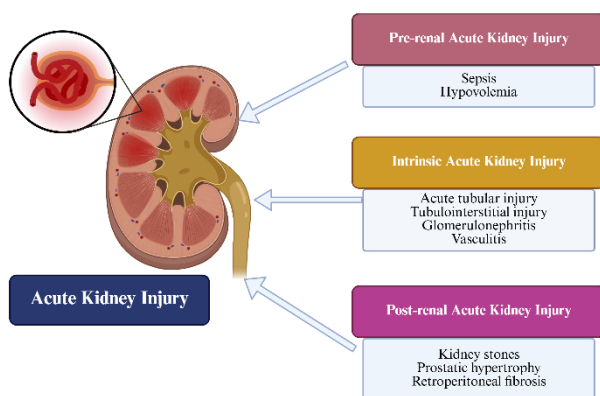


Fig.1: Causes of Acute kidney Injury

III. RISK FACTORS

It is possible for people with AKD to experience a decline in their quality of life, impairment, cardiovascular events, and an increase in death rates, among other potential complications. There are a number of patient characteristics that can raise the

probability of developing AKD[19]. Some of these variables include age, race, genetics, hypertension, diabetes, and metabolic syndrome. The intensity, duration, and frequency of acute kidney injury are also risk factors for chronic kidney disease[20]. It was discovered by Kellum et al. that the severity of acute kidney injury (AKI), as measured by the KDIGO criteria, is a powerful indication of the development of chronic kidney disease (CKD). According to the findings of an investigation conducted by Thakar et al. on 3,679 diabetic adults, episodes of acute renal damage were associated with an increased risk of developing chronic kidney disease (CKD)[21].

The risk of acute kidney disease (AKD) can be reduced by modifying certain factors, such as being older, having a medical history that includes operations, coronary angiography, COVID-19, fluid overload, and some pharmaceutical agents, such as chemotherapeutics and nonsteroidal anti-inflammatory drugs (NSAIDs)[22]. A single-center cohort of 6,101 patients with stage 3B-5 chronic kidney disease was looked at by Chou et al. between the years 2005 and 2018. They discovered that older patients had a higher risk of developing acute kidney injury (AKI) and progressing to end-stage kidney disease (ESKD) than younger patients. As a result of doing an analysis on 29,388 individuals who had undergone heart surgery, Ishani and colleagues came to the conclusion that even moderate increases in blood creatinine levels following cardiac surgery were indicative of an increased likelihood of developing chronic kidney disease (CKD) in the future[23]. Acute kidney injury (AKI) during coronary angiography was found to be associated with an elevated risk of long-term renal function loss in 11,249 persons in Canada who were 18 years of age or older and had the operation done. The study was conducted by James and colleagues. Notably, Hadadi et al. claimed that COVID-19-associated acute kidney injury (AKI) may have a long-term impact on the continuance of renal impairment in a recent cohort analysis of 1,017 patients who had ever been hospitalized but made it to the day of discharge[24].

Patients who were critically ill and had ever sought the advice of a specialist for acute kidney injury (AKI) while they were in the intensive care unit were the subjects of a comprehensive observational study that was carried out across five different locations in the United States. There was a wide range of demographics represented among the patients[25]. The authors Bouchard et al. At the time of the diagnosis of acute kidney injury (AKI), they found no link between the recovery of kidney function and fluid overload, which is defined as a 10% rise in body weight relative to baseline. Peak serum creatinine concentrations that occurred at the same time as fluid overload were less likely to occur in patients whose renal function was restored (35% versus 52%, $p = 0.007$). This was the case for patients who had their renal function restored. Cancer, on the other hand,

can both induce and arise from acute kidney injury and chronic kidney disease. The use of nephrotoxic chemotherapy medicines can make kidney disease worse, and the use of certain newer chemotherapeutic agents can also cause a decline in renal function after they have been administered. In order to lessen the kidney damage caused by chemotherapy, it is necessary to properly diagnose and treat the condition[26].

IV. ROLE OF THE RENAL VASCULATURE IN ACUTE KIDNEY INJURY

During the course of kidney development, interactions between metanephric mesenchyme and ureteric epithelium take place. Within the metanephric mesenchyme, there are two branches that can be found: the renal stroma and the nephrogenic mesenchyme[27]. The formation of the main renal interstitium takes place during the process of kidney development. This occurs when the renal stroma interdigitates with the nephron progenitor caps and the branches of the ureteric bud. There are many different types of vascular supporting cells that originate from the renal stroma. Some of these cells include pericytes, fibroblasts, renin-producing cells, mesangium, and endothelial progenitors[28].

By way of the circulatory system, approximately twenty percent of the heart's output is sent to the kidneys. This process, known as angiogenesis, is responsible for the development and invagination of new blood vessels. Specifically, it is the point at which the vascular system begins. Endothelial precursors, which are already present in the kidney mesenchyme, are responsible for initiating the process of vascular development, also known as vasculogenesis[29]. This process ultimately results in the establishment of a patent vascular system by linking with the angiogenic arteries. Although the precise process by which the renal vasculature is produced is unknown, it is known that it involves a combination of angiogenesis and vasculogenesis[30]. A subset of the renal endothelium that was created from the renal stroma and was recognized by the *Foxd1* gene was shown to be the origin of peritubular capillaries, according to research that was conducted in the past by our group[31].

A transcription factor that is found in stromal cells is known as *Foxd1*, which is the initial hallmark of renal stroma. There are a number of abnormalities that can be observed in kidneys that have a *Foxd1* deletion. These include a reduction in the number of nephrons, an uneven renal capsule, misplaced vasculature inside the renal capsule, and an overall incorrect patterning of renal structures. At the same time, the ureteric bud has fewer branches. *Foxd1* may play a role in maintaining the right orientation of the renal vasculature, according to recent data.

V. MECHANISM OF ANGIOGENESIS IN ACUTE KIDNEY INJURY

It is anticipated by experts that by the year 2040, chronic kidney disease (CKD) will have exceeded all other causes of mortality across the globe[32]. The prevalence of CKD is on the rise. The great majority of instances of chronic kidney disease (CKD) are caused by metabolic (such as diabetes) and vascular variables. However, genetics, immunology, and vascular factors are all potential contributors to the development of CKD. A number of different molecular pathways and mediators are involved in the progression of kidney disease[33]. Individuals who have chronic kidney disease (CKD) are at a greater risk of experiencing acute kidney injury (AKI), mortality, and the progression of chronic kidney disease (CKD), independent of the source of CKD. In addition to renal (parenchymal cell injury), prerenal (decreased perfusion), and postrenal (obstructed urinary tract) causes of acute kidney injury (AKI), there are additional potential causes[34]. Potential renal reasons include obstruction that is either untreated or has been present for an extended period of time, decreased perfusion, tubular, glomerular, and interstitial damage. The growing global burden of kidney disease is exacerbated by the lack of a comprehensive collection of early diagnostic biomarkers and effective treatments for acute kidney injury (AKI) and chronic kidney disease (CKD)[35]. Therefore, in order to create new biomarkers and treatments that can improve the outcomes of renal illnesses, it is necessary to have a more in-depth understanding of the mechanisms that cause damage to the kidneys and the processes that repair them[36]. The relationship between AKI and CKD has been demonstrated to exist. The evolution of acute kidney injury (AKI) and AKI in general is sped up by chronic kidney disease (CKD), particularly bouts of AKI that are severe or recurring, which are themselves caused by CKD[37]. Other than the severity and duration of acute kidney injury (AKI), there are presently no reliable biomarkers that can predict the transition of acute kidney injury (AKI) to chronic kidney disease (CKD). This makes it difficult to recruit patients with early-stage AKI for clinical studies that aim to prevent the progression of AKI to acute kidney injury (AKI)[38]. The fact that even seemingly reversible causes of acute kidney injury (AKI), such as blockage, can proceed to chronic kidney disease (CKD) if the obstruction is not removed within a certain amount of time has been well-documented through experimental research. At the moment, the failure of serum creatinine to decrease is the most prominent early indicator of the transition from acute kidney injury to chronic kidney disease. However, because this event takes place at a later stage, it is not possible to undertake preventive treatments when acute kidney injury is recognized[39]. The risk of impaired kidney repair following acute kidney injury (AKI) and/or the harmful influence of preexisting chronic kidney

disease (CKD) on renal repair becomes a matter for concern as a result of this. In spite of the fact that adult kidneys have a relatively low cell turnover rate, they actually exhibit repair mechanisms following acute kidney injury (AKI)[40]. Concerning the specific manner in which mature cells that have undergone dedifferentiation contribute to kidney repair in comparison to specialized resident cells of renal progenitor, there is currently a lack of consensus pertaining to this matter. Furthermore, the organ may be in danger due to the molecular signs of acute kidney injury (AKI) as well as the biological processes that are associated with attempted repairs that are unsuccessful.

Following the cell death that is characteristic of the acute phase of acute kidney injury (AKI), the remaining cells enter a recovery phase that involves the activation of protective and regenerative mechanisms. This phase is an important part of the healing process. During this phase, the epithelial cells will have their characteristics and functions restored to their previous state. On the other hand, fibrosis and the slow loss of kidney function can be the result of epigenetic modifications that promote inflammation and the release of a profibrogenic secretome. Additionally, fibrosis can be caused by cell senescence, inadequate epithelial-mesenchymal transition (EMT), and G2/M cell-cycle arrest (CCA). Different molecular pathways each play a part in the regulation of the angiogenesis process[41]. Mechanism of Angiogenesis in Acute Kidney Injury mentioned in Fig.2.

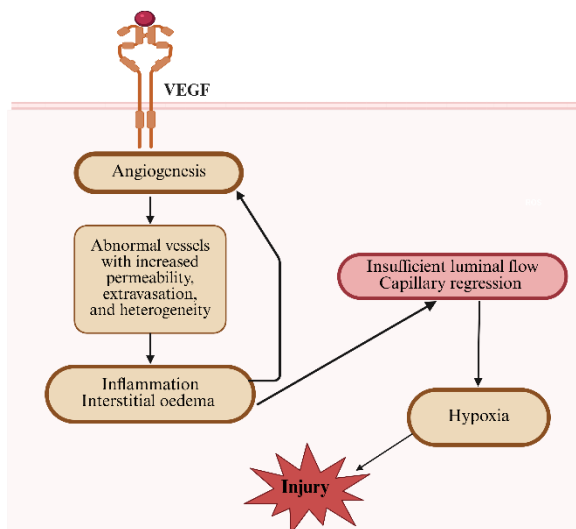


Fig.2: Mechanism of Acute kidney Injury

VI. VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) PATHWAY

Angiogenesis, which is the process of forming and repairing new blood vessel structures, is essential to both the normal function of tissues and the development

of diseases such as cancer and inflammation[42-44]. There have been various signaling molecules that have been shown to have important roles in the process of angiogenesis during the course of the last few decades. The VEGF-VEGFRs, the ephrin-Eph receptors, the angiopoietin-Tie combination, and the Delta-Notch system are all examples of these[45]. Vascular endothelial growth factors (VEGFs) and receptors (VEGFRs) are responsible for regulating both the creation of blood vessels from precursor cells during early embryogenesis and the generation of blood vessels from pre-existing vessels at a later stage[46]. Both of these processes take place throughout the embryonic developing stage. On the other hand, the VEGFR gene family in vertebrate animals only consists of three or four members, whereas the VEGF gene family contains at least seven members, one of which is VEGF-E, which is derived from the viral genome[47]. In both normal and malignant angiogenesis, including angiogenesis in tumors, VEGF-A and its receptors, VEGFR-1 and VEGFR-2, play significant roles[48]. These receptors are responsible for the formation of blood vessels. VEGF-C/D and VEGFR-3 are largely responsible for regulating lymphangiogenesis; however, they are also capable of influencing angiogenesis during the early stages of embryogenesis[49].

VII. HYPOXIA-INDUCIBLE FACTOR (HIF)

It is referred to as hypoxia when there is a drop in the physiological level of oxygen. Cellular dysfunction is the result of this condition, which can be brought on by vascular and pulmonary diseases, or it can be brought on by encouraging the creation of cancerous tissue[50]. There are three different types of hypoxia that can occur in the blood: acute hypoxia, chronic hypoxia, and hypoxia following reperfusion[51]. Chronic hypoxia. Under situations of limited oxygen transport brought on by chronic hypoxia (oxygen tension, 2-3%), cells grow in an uncontrollable manner. This is especially true in the case of cells[52]. On the other hand, aberrant blood vessel closure and subsequent reversal of blood flow are induced by acute hypoxia that is specific to the vasculature of the tumor, particularly when reperfusion is being performed. If this is the case, then increasing blood flow in order to restore the physiological oxygen level will still result in an excess of oxygen[53]. This excess oxygen will then cause damage to tissues, an increase in free radicals, and the simultaneous activation of genes that respond to stress. This phenomenon is referred to as "reoxygenation injury" in the body. In chronic hypoxia, normal cells and tissues perish as a result of the prolonged low oxygen levels[54]. On the other hand, tumor cells are able to continue growing in the hypoxic zone because they are able to adapt and undergo genetic modifications that make them resistant to low oxygen levels. Induction of

angiogenic and growth factors, which brings about the creation and proliferation of new blood vessels, is one of the hypoxic responses that has received the most attention from researchers and is also one of the most common[55]. Angiogenesis and arteriogenesis are the two most prevalent techniques of blood vessel growth. These processes involve the sprouting and collateral expansion of mural cells, which results in the formation of collateral bridges across arterial networks. Vasculogenesis, on the other hand, is the process by which blood vessels are formed from endothelial progenitors[56]. An extension of the vascular bed is the result of relative hypoxia, which occurs when tissues expand beyond their normal oxygen diffusion limit. This is due to the fact that the cells that line the vascular beds are physiologically oxygenated by the process of simple diffusion of oxygen, and the relative hypoxia stimulates angiogenic factors. VEGF is one of the most remarkable angiogenic factors because of its capacity to activate angiogenesis in a dose-dependent manner. This ability makes it one of the most important angiogenic factors[57].

VIII. ANGIOPOIETIN TIE SIGNALLING

The angiopoietin (Ang)-Tie signaling pathway has an effect on a variety of vascular processes, including development, angiogenesis, remodeling, modification of vascular permeability, homeostasis, quiescence, and stability throughout vascular development[58]. Over the course of the past ten years, a significant amount of research has been conducted on the angiopoietin-Tie signaling pathway in an effort to uncover possible therapy targets for a variety of illnesses. One of the factors that has been linked to peripheral artery disease, atherosclerotic plaque development, vascular dysfunction, and ischemia/reperfusion injury in the cardiovascular system is the dysregulation of the angiopoietin-Tie signaling axis[59]. Within the context of ocular diseases including diabetic macular edema and wet age-related macular degeneration, the Angiopoietin-Tie signaling pathway is an essential component in the regulation of choroidal and retinal neovascularization, as well as the regulation of vascular leakage processes. In addition, researchers are highly interested in the role that Tie2 plays in the development of cancer and inflammation. Angiopoietin-1, also known as Ang1, is yet another neuroprotective medication that has recently been the subject of research on its capacity to avert the occurrence of brain death[60].

The angiopoietin family is comprised of the proteins Ang1, Ang2, Ang3, and Ang4, all of which exhibit a connection to the Tie2 receptor. Ang1 and Ang2 are the major ligands that are associated with Tie2. It is not known what the biological functions of the human and mouse orthologs Ang3 and Ang4 are because they have received less research[61]. Blood arteries that

are completely formed and sedentary secrete Ang1, which is a natural agonist of Tie2. This agonist facilitates the stability of the blood vessels by attaching to and activating Tie2. It has been thought for a long time that Ang2, which is frequently produced in arteries that are either ill or remodeling, performs the function of an antagonist by decreasing Ang1 binding in a competitive manner[62]. In light of recent discoveries that it can perform the function of an agonist under certain conditions, it is highly probable that the role of Ang2 is highly reliant on the overall context. When it comes to natural Ang1 oligomerization, the most prevalent types are tetramers and higher-order multimers[63]. On the other hand, dimers, trimers, and tetramers are the most common forms of native Ang2 oligomerization. In order for the ligand to be activated by Tie2, it must be in its tetrameric form, which is the lowest oligomeric form[64]. Activation and trafficking are two examples of Tie2 ligand-specific responses that are influenced by the oligomerization state of the ligand involved[65]. When Tie2 is activated by either Ang1 or Ang2, the results include the release of ligands and the internalization of receptors. The process of dephosphorylating Tie2, which in turn controls its activation, is carried out by a protein known as vascular endothelial protein tyrosine phosphatase (VE-PTP)[66].

IX. ENDOTHELIAL PROGENITOR CELLS

In spite of major breakthroughs, cardiovascular disease (CVD) continues to be the leading cause of mortality around the world. It has been demonstrated that the utilization of embryonic stem cells or endothelial progenitor cells (EPCs) in stem cell or progenitor cell treatment has the potential to significantly increase the regeneration of damaged vascular and cardiac tissues. On the other hand, there is a significant amount of study being conducted because the fundamental mechanisms are not yet completely known. In both laboratory and animal research, vascular endothelial growth factor (VEGF), which is one of the most well-known pro-angiogenic agents, has been shown to stimulate the development of new blood vessels. In addition to controlling hematopoietic cell trafficking and key developmental consequences, it has been demonstrated that the stromal cell-derived factor-1 α (SDF-1 α)/CXCL12-CXCR4 chemokine ligand-receptor axis plays a role in promoting tissue regeneration. This is accomplished by mediating the recruitment of progenitor cells into ischemic areas. However, despite the fact that it is well-established that CXCL12 plays a role in the recruitment of endothelial progenitor cells along hypoxia gradients, which is driven by HIF-1 α , the significance of CXCL12 in the development of vessels has remained ambiguous[64]. It is widely acknowledged that CXCL12 plays a crucial part in the trafficking of hematopoietic and lymphopoietic stem cells, as well as stem cell

progenitors. This is in addition to the fact that it improves cell survival, proliferation, and differentiation. Not only does it play a significant part in the process of repairing the vascular wall after an injury, but it also promotes the development of new blood vessels and new blood vessels[65].

The ELR motif-containing CXC chemokine keratinocyte-derived growth factor (KC) or CXCL1, which is an ortholog of human CXCL8/interleukin-8 (IL-8), is also a potent angiogenic agent. This is despite the fact that it is most commonly known for its chemotactic effect toward neutrophils and monocytes/macrophages. With regard to cardiovascular illness, KC/CXCL8 is an essential component in the process by which the endothelium recovers from vascular injury. This recovery is accomplished by a mechanism that is dependent on CXCR2. In recent years, it has been proven that macrophage migration inhibitory factor (MIF), which is a pleiotropic inflammatory cytokine with chemokine-like properties, can function as an alternative ligand of CXCR2 and CXCR4, which is not the same as its corresponding receptors. The MIF/CXCR2 axis has a significant amount of effect on the recruitment of atherogenic monocytes and inflammatory neutrophils[66]. On the other hand, the MIF/CXCR4 axis plays a role in the recruitment of atherogenic T cells and in the migration of fibroblasts. It is important to note that MIF, which is secreted bimodally by endothelial cells in response to hypoxic stimulation, is responsible for enhancing EPC chemotaxis in a manner that is dependent on CXCR4. The relationship between MIF and CXCR2/4 is responsible for the regulation of atherogenesis, in addition to its more generalized participation in the process of tumor angiogenesis.

An initial investigation was conducted by Asahara and colleagues, in which they extracted endothelial progenitor cells from peripheral blood samples of human subjects by using anti-CD34 magnetic microbeads. After that, Hur et al. created two separate types of extracellular polymer cells (EPCs) from adult peripheral blood. These EPCs are classified as early EPCs, which are extremely adhesive but have a low capacity for proliferation, and late EPCs, which are extremely weakly adherent but exhibit remarkable proliferating capabilities. Recently, it was shown that embryonic endoplasmic reticulum cells (eEPCs) are capable of providing cardioprotection against acute ischemia-reperfusion injury in preclinical animals[67].

X. THERAPEUTIC APPLICATIONS TO ENHANCE ANGIOGENESIS AND VASCULAR REPAIR

It is possible to establish therapeutic angiogenesis with the administration of a wide range of angiogenic factors, including but not limited to VEGF, FGF, PDGF, TGF- β , TNF- α , the angiotensins, and

CXC chemokines[68]. The heparin-binding dimeric glycoprotein known as VEGF, which has a molecular weight of 45 kDa, is secreted by almost every type of cell available. In spite of this, they are commonly considered to be mitogens that particularly target endothelial cells. This is due to the fact that the bulk of VEGF binding sites are found in these cells[69]. Quiescent cells and proliferative cells are both included in this category. Two ways that can be utilized to directly administer VEGF include intravenous injections and intracoronary injections. Due to the fact that the dose and effective concentration from injections are rather low, it is possible to administer it after it has been incorporated into a variety of polymeric drug delivery systems or after it has been encapsulated in micro or nanocarriers[70]. On the other hand, fibroblast growth factor (FGF) exhibits its ability to induce angiogenesis by binding to a number of receptors that are located on the surface of endothelial cells. These receptors include integrins, heparan-sulfate proteoglycans, and tyrosine kinase receptors[71]. To further complicate matters, inflammatory cytokines and chemokines, vascular endothelial growth factor (VEGF), and fibroblast growth factors (FGFs) all collaborate to influence the formation of blood vessels. Previous research has demonstrated that injectable polyvalent coacervates that contain polycations, heparin, and fibroblast growth factor-2 (FGF2) are capable of promoting angiogenesis[72]. Interestingly, a single injection of 500 ng of FGF2 in the coacervate was sufficient to stimulate angiogenesis in vivo. This means that the injection was only necessary once.

Research on therapeutic angiogenesis has progressed to the point where it is now possible to induce embryonic vasculogenesis in animal models that are designed to imitate vasculature. Implants made of MatrigelTM and biological extracellular matrix (ECM) are used in conjunction with endothelial and mesenchymal cells or progenitors in order to accomplish this goal[73]. The majority of the cells that are utilized in the process of therapeutic angiogenesis originate from adult vascular cells that have been obtained through the use of routine sampling procedures. The endothelial cells, the vascular smooth muscle cells, and the pericytes are all included in this group of cells. Endothelial progenitor cells (EPCs) and bone marrow mesenchymal stem cells (BMMSCs) are two additional cell types that have been the subject of substantial research for the purpose of therapeutic angiogenesis[74]. Through the utilization of fibrin-based scaffolds that contained BMMSCs, the neovascularization process was effectively accelerated in myocardial that had been chronically infarcted. With the ability to migrate to the increasing vasculature in the circulation, endothelial progenitor cells, also known as EPCs, are able to repair damaged blood vessel walls. In addition, stem cells may have a role in the process of angiogenesis, which is another putative function. Following a myocardial

infarction, mice whose mesenchymal stem cells (MSCs) had elevated levels of SDF-1 α were able to enhance their heart function by means of angiogenesis[75].

Endothelial dysfunction, microvascular rarefaction, and decreased blood flow are all factors that contribute to the progression of chronic kidney injury (CKI), which is why vascular restoration is the most important condition to treat[76]. A number of different therapy techniques have been examined in order to enhance vascular regeneration and protect endothelial integrity in patients with chronic kidney injury (CKI). Endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs) are two examples of cellular treatments that have the ability to restore vascular homeostasis. These treatments work by promoting angiogenesis, reducing inflammation, and improving endothelial function. Enhanced endothelium regeneration and decreased oxidative stress are two additional ways in which stem cell exosome therapy can help improve vascular repair. MicroRNAs and growth factors can be delivered to the bloodstream using this method.

In order to facilitate the process of neovascularization and protect the renal microvasculature from the harmful effects of ischemia, gene therapy utilizes many strategies, including the regulation of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 α (HIF-1 α). The utilization of biomaterials and procedures that are based on nanotechnology has the potential to improve the localized distribution of antibiotics and medications that promote angiogenesis and inflammation. Another illustration of this would be the medication delivery devices that are based on hydrogel. One further illustration is the targeted therapy that is mediated by nanoparticles. Antioxidants, angiotensin-converting enzyme (ACE) inhibitors, and statins are examples of pharmacological interventions that facilitate the restoration of endothelial function. These medicines work by lowering levels of oxidative stress, inflammation, and fibrosis. Microvascular perfusion can be improved with hyperbaric oxygen therapy (HBOT), and shear stress-induced vascular remodeling can be improved through mechanical and lifestyle therapies such as regulated exercise[77]. The reduction of chronic inflammation and fibrosis, which is beneficial to the healing of the vascular system, can be accomplished through immunomodulation strategies such as the polarization of macrophages and the regulation of T cells. Because of developing technologies such as artificial intelligence-driven personalized medicine and CRISPR-based gene editing, there is reason to be optimistic about the future of vascular-targeted treatments in chronic kidney disease (CKD). These multidisciplinary treatments have as their main objectives the restoration of endothelial function, the improvement of microvascular healing, and the slowing of the course of chronic kidney injury (CKI).

XI. CONCLUSION

During the recovery process following acute kidney injury (AKI), angiogenesis and vascular repair are essential components. Additionally, a number of signalling pathways are responsible for coordinating endothelial regeneration and capillary restoration. Endothelial progenitor cells, vascular endothelial growth factor (VEGF), hydrophilic factor-1 α (HIF-1 α), and angiopoietins interact with one another to determine the extent of vascular repair and functional recovery. There is a significant risk of uncontrolled angiogenesis leading to fibrosis and chronic renal impairment, despite the fact that there is the possibility that pro-angiogenic interventions could improve renal function. Therapeutic treatments should encourage controlled angiogenesis and microvascular stability, with an emphasis on fostering controlled angiogenesis and microvascular stabilisation. This will help to avoid the difficulties that are described above. This will ensure that the renal system recovers more effectively without creating any long-term damage. It is necessary to conduct additional study in order to enhance and improve these methods.

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