Cytotherapy, 2017; 19: 333–348

International Society for Cellular Therapy
ISCT®

REVIEW ARTICLE

Stem cell therapy: An emerging modality in glomerular diseases

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Abstract

The kidney has been considered a highly terminally differentiated organ with low proliferative potential and thus unlikely to undergo regeneration. Glomerular disease progresses to end-stage renal disease (ESRD), which requires dialysis or renal transplantation for better quality of life for patients with ESRD. Because of the shortage of implantable kidneys and complications such as immune rejection, septicemia and toxicity of immunosuppression, kidney transplantation remains a challenge. Therapeutic options available for glomerular disease include symptomatic treatment and strategies to delay progression. In an attempt to develop innovative treatments by promoting the limited capability of regeneration and repair after kidney injury and overcome the progressive pathological process that is uncontrolled with conventional treatment modalities, stem cell–based therapy has emerged as novel intervention due to its ability to inhibit inflammation and promote regeneration. Recent developments in cell therapy have demonstrated promising therapeutic outcomes in terms of restoration of renal structure and function. This review focuses on stem cell therapy approaches for the treatment of glomerular disease, including the various cell sources used and recent advances in preclinical and clinical studies.

Key Words: *adult stem cells, embryonic stem cells, end stage renal disease, glomerular disease, regeneration, stem cell therapy*

Introduction

The kidney is a complex organ consisting of a variety of cells, including glomerular podocytes, endothelial cells, mesangial cells, interstitial cells, tubular epithelial cells and connecting duct cells. The kidney functions efficiently with these cell varieties, which interact to establish a precise cellular environment [1]. The functions of the kidney are (i) excretion of waste products; (ii) regulation of pH, electrolytes and systemic fluid volume; (iii) maintenance of systemic blood pressure; and (iv) production of erythropoietin [2]. These are performed by the functional units of the kidney, the nephrons. Nephron development in mammals requires differentiation of a renal progenitor population of mesenchymal cells into epithelial cells. After the outgrowth of ureteric bud, mesenchymal cells aggregate near the tip of newly formed branches, undergo mesenchymal to epithelial differentiation and establish the renal vesicle, the precursor for the glomerular and renal tubule compartment [3]. The distal aspects of the branched duct therefore represent the niche for renal progenitors undergoing mesenchymal to epithelial transition [4]. In the adult kidney, this nephrogenic mesenchymal progenitor population disappears, possibly due to the loss of its niche [5].

Renal failure is a global health issue, with 8–16% of the adult population suffering from chronic kidney disease (CKD), defined as a reduced glomerular filtration rate and increased albuminuria [6]. Renal failure because of acute kidney injury (AKI) is defined as a sudden increase in serum creatinine concentration and decreased urine output, which often progresses to CKD [7,8]. AKI is often associated with multi-organ damage

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(Received 23 June 2016; accepted 3 November 2016)

ISSN 1465-3249
http://dx.doi.org/10.1016/j.jcyt.2016.11.003

in the hospital setting. Despite current therapeutic modalities, mortality ranges from 30% to 80% when associated with multi-organ failure [9–11]. Recovery of renal function after AKI is dependent on the replacement of necrotic tubular cells with functional tubular epithelium [12,13]. Absence or reduction of epithelial and endothelial cell regeneration may predispose to tubulo-interstitial renal scarring and CKD [14,15], eventually requiring organ replacement in these patients. Lack of viable functional renal structures contributes to inefficient recovery, leading to high morbidity.

Glomerular diseases (GDs) include acute proliferative glomerulonephritis (GN), rapidly progressive GN, minimal change disease, membranous GN, membranoproliferative GN, focal segmental glomerulosclerosis (FSGS) and immunoglobulin (Ig)A nephropathy. GD can present as nephrotic syndrome, nephritic syndrome, rapidly progressive renal failure, diabetic/hypertensive nephropathy, AKI, CKD and isolated proteinuria or hematuria, which gradually lead to renal failure [5]. GDs may be primary or secondary due to systemic/autoimmune diseases and are believed to share an immune-mediated pathogenesis [16]. This is the common cause of end-stage renal disease (ESRD) worldwide, but particularly in developing countries such as India and China [17]. Therapeutic options for GDs primarily include symptomatic treatment and strategies to delay progression toward renal failure. Traditional immunosuppressive therapies for GDs include corticosteroids and cytotoxic agents, which have been used since the 1950s [18]. Current immunosuppressive therapies for GDs are not uniformly effective and are frequently associated with serious side effects [19]. Unfortunately, due to marked paucity of organs, the pool of patients with GDs who progress to ESRD continues to rise worldwide. Dialysis and renal transplantation are the two therapeutic modalities for these patients. Dialysis compromises quality of life and does not replace all renal functions, and renal transplantation is not always possible because of the lack of compatible organ donors [20].

To achieve better treatment options for GDs, it is necessary to find strategies to regenerate the kidney. Renal tubules are able to regenerate spontaneously, but the glomeruli cannot recover spontaneously from a major injury [21]. This finding suggests that the reservoir of cells with plasticity that are able to regenerate the glomeruli is probably enough to support normal cell turnover but is insufficient to intervene in cases of major tissue losses. Stem cell (SC)-based therapies have the potential to ameliorate many diseases, including kidney diseases, and have been proven to be safe and effective in the treatment of a wide range of immune-mediated diseases as well. Stem cell therapy (SCT) for kidney injury and diseases has been intensively studied recently. The SCT field is advancing rapidly and evolving as a future therapeutic modality for GD. SCs are defined as cells that are capable of self-renewal and can differentiate into a variety of phenotypes [22]. The first study of SCs in experimental GN was published in 1999 by Imasawa *et al.*, who performed bone marrow transplantation on a murine model of IgA nephropathy [23]. Since that time, many preclinical and clinical studies have been performed that support the ability of various SC populations to have the therapeutic effect on GDs. The purpose of this article is to review the studies performed on the use of SCs and progenitor cells in GDs, both at the experimental and clinical levels, and to discuss the mechanism underlying the beneficial effect of SCs and its possible translation to therapeutic approaches for clinical applications. Recent advances in SC biology and cell culture techniques have facilitated the development of SCT for clinical translation. Compared with other approaches, SCT can be more practically applied to renal treatment due to the relatively simple process of cell manipulation, easy access to the specific site in a less invasive manner and effective integration with the host tissues by infused cells. The main goal of renal regenerative medicine by SCT is to achieve and sustain the recovery of altered renal functions after kidney injury [24]. Cell therapy involves "immunological resetting" in which the reproducibility of SCs is restored under strict proliferation controls to generate sufficient quantities of tissue or cells by differentiation into the desired cell type(s) with surrounding tissue integrity, leading to prolonged survival, even after transplantation, without any adverse effect.

Potential options for renal repair

CKD can result from a variety of factors, including genetic and environmental. These progress to ESRD, requiring replacement of injured cells or tissue. To solve this problem, researchers have been investigating novel regenerative options (Figure 1), including repair or replacement of the damaged organ. Therapies for renal repair include the stimulation of endogenous repair *in situ*, delivery of adult SCs from other organs or the isolation and redelivery of an endogenous renal SCs [25]. Stimulation of endogenous repair may simply require the stimulation of an endogenous SC population, if one exists, or the promotion of tubular turnover and the resolution of inflammation. *De novo* organ replacement, involving either an engineered device or the construction of chimeric replacement organ using tissue from other animals, is also being investigated and reviewed [25].

SC strategies for renal repair

The putative events leading to renal repair via SCs are protective actions by paracrine factors, including proteins